Diabetes: What's new?

Natasha Garfield, MDCM, FRCP(C)
Endocrinologist, MUHC
May 6, 2022

Disclosures

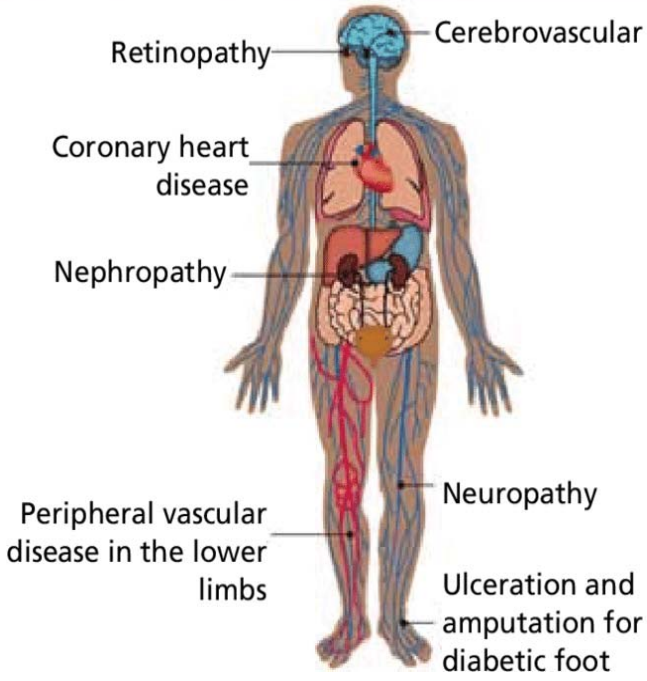
- Nothing to disclose

Objectives

- By the end of this presentation participants will be able to:

- Become familiar with a new class of drugs: the dual GLP-1/GIP agonists in the treatment of type 2 diabetes mellitus
- Become familiar with new technologies available in the management of patients with diabetes
- Be able to identify patients in their practice who might benefit from the above therapies

Chronic Complications of Diabetes Mellitus



ALSO:

- NASH/cirrhosis
- Cancers
- Cognitive decline
- OSA
- Hip fractures
- Imbalance and fragility
- Joint complaints
- ED
- Sexual dysfunction
- Infertility
- Gut problems

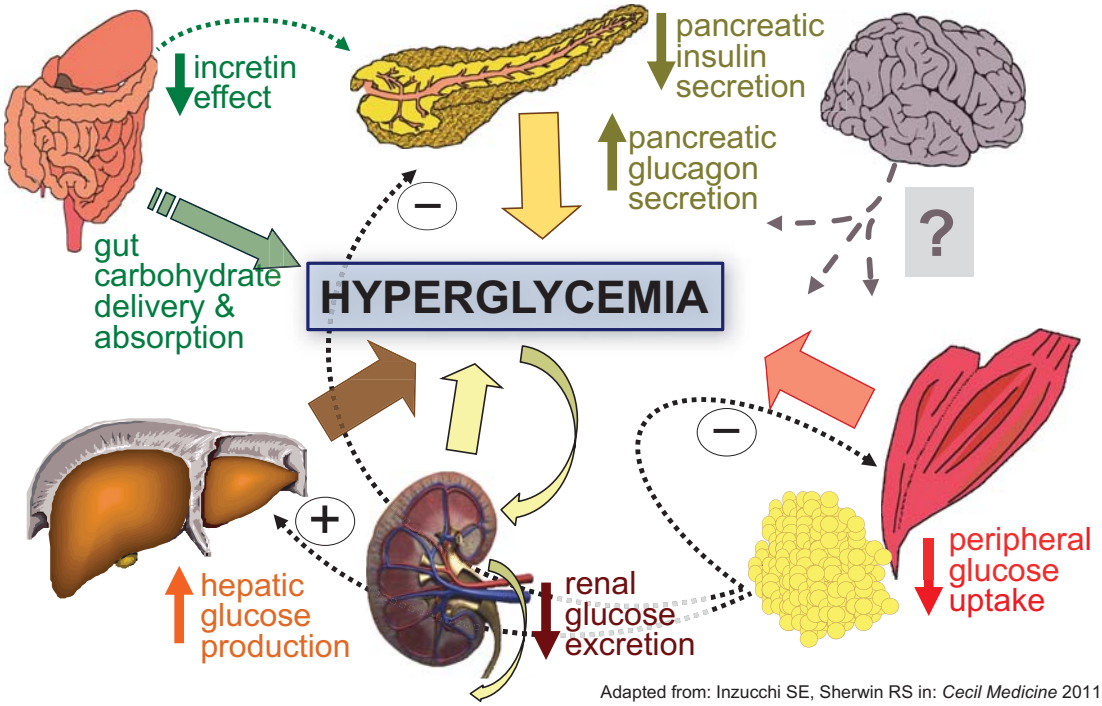
A1C Targets

2018

≤6.5	Adults with type 2 diabetes to reduce the risk of CKD and retinopathy if at low risk of hypoglycemia
≤7.0	**MOST ADULTS WITH TYPE 1 OR TYPE 2 DIABETES**
7.1 ↓ **8.5**	**7.1-8.0%**: Functionally dependent* **7.1-8.5%:** • Recurrent severe hypoglycemia and/or hypoglycemia unawareness • Limited life expectancy • Frail elderly and/or with dementia**
Avoid higher A1C to minimize risk of symptomatic hyperglycemia and acute and chronic complications	
End of life	A1C measurement not recommended. Avoid symptomatic hyperglycemia and any hypoglycemia

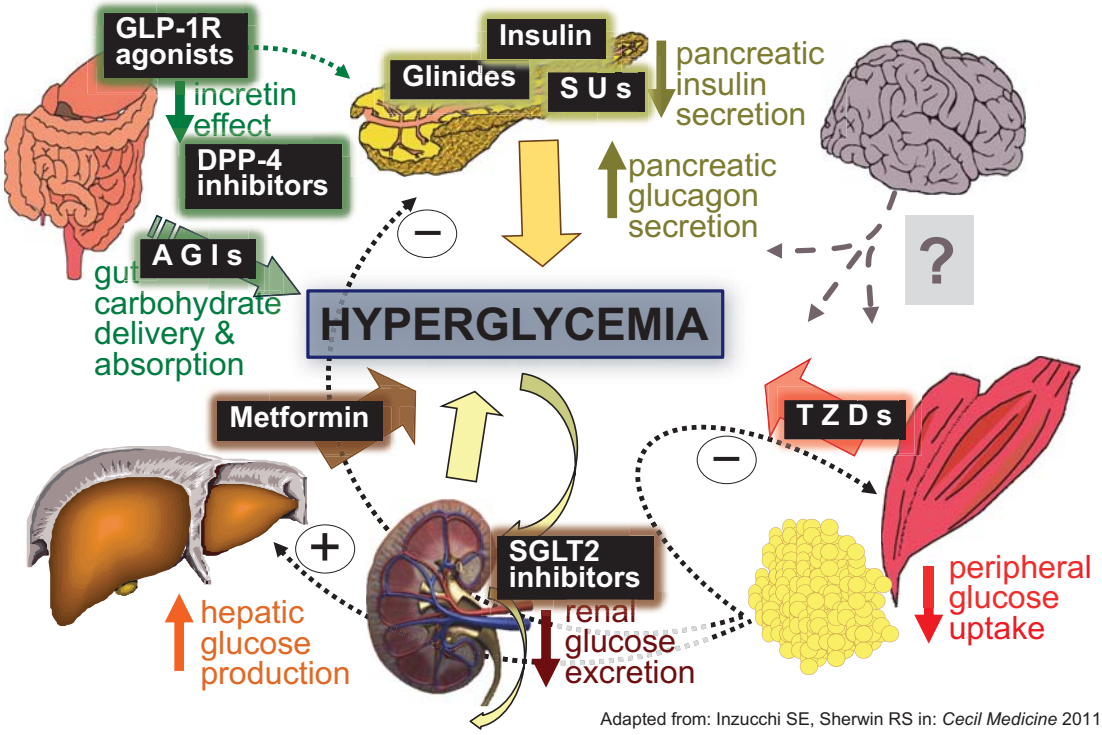
* Based on class of antihyperglycemic medication(s) utilized and person's characteristics
** see Diabetes in Older People chapter
CKD; chronic kidney disease

Multiple, Complex Pathophysiological Abnormalities in T2DM



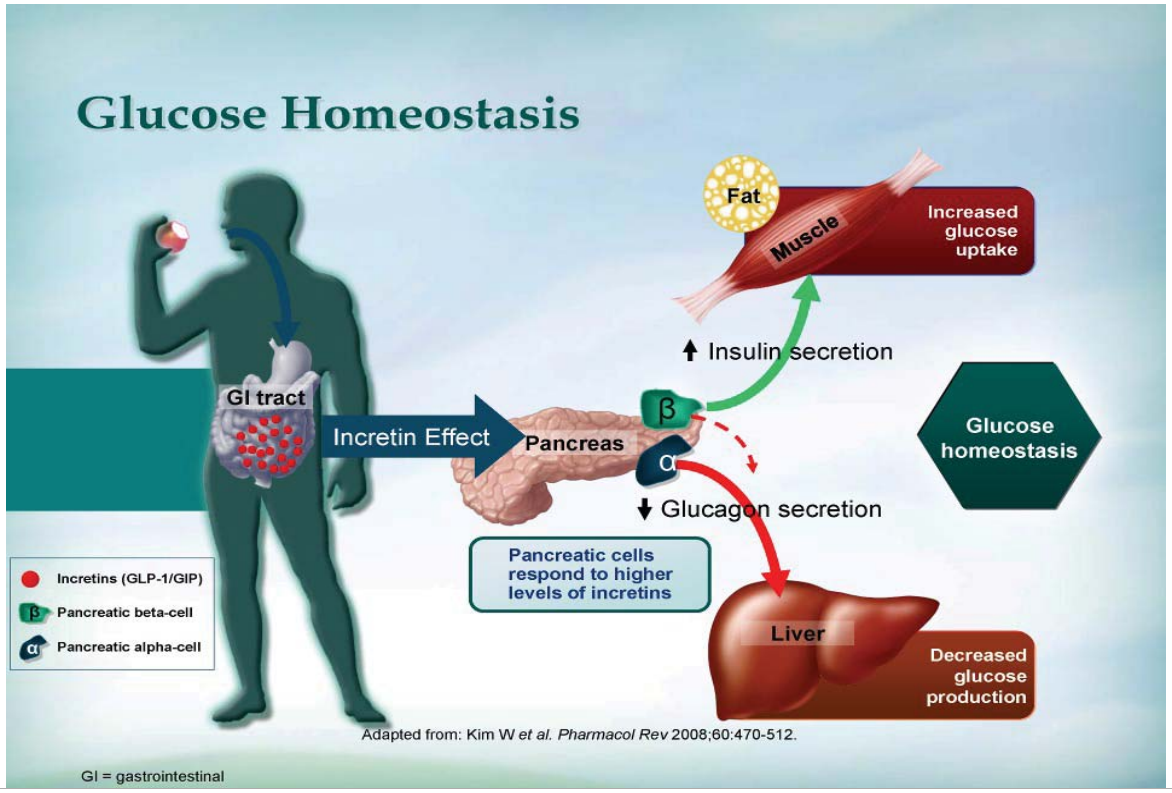
Adapted from: Inzucchi SE, Sherwin RS in: *Cecil Medicine* 2011

Multiple, Complex Pathophysiological Abnormalities in T2DM



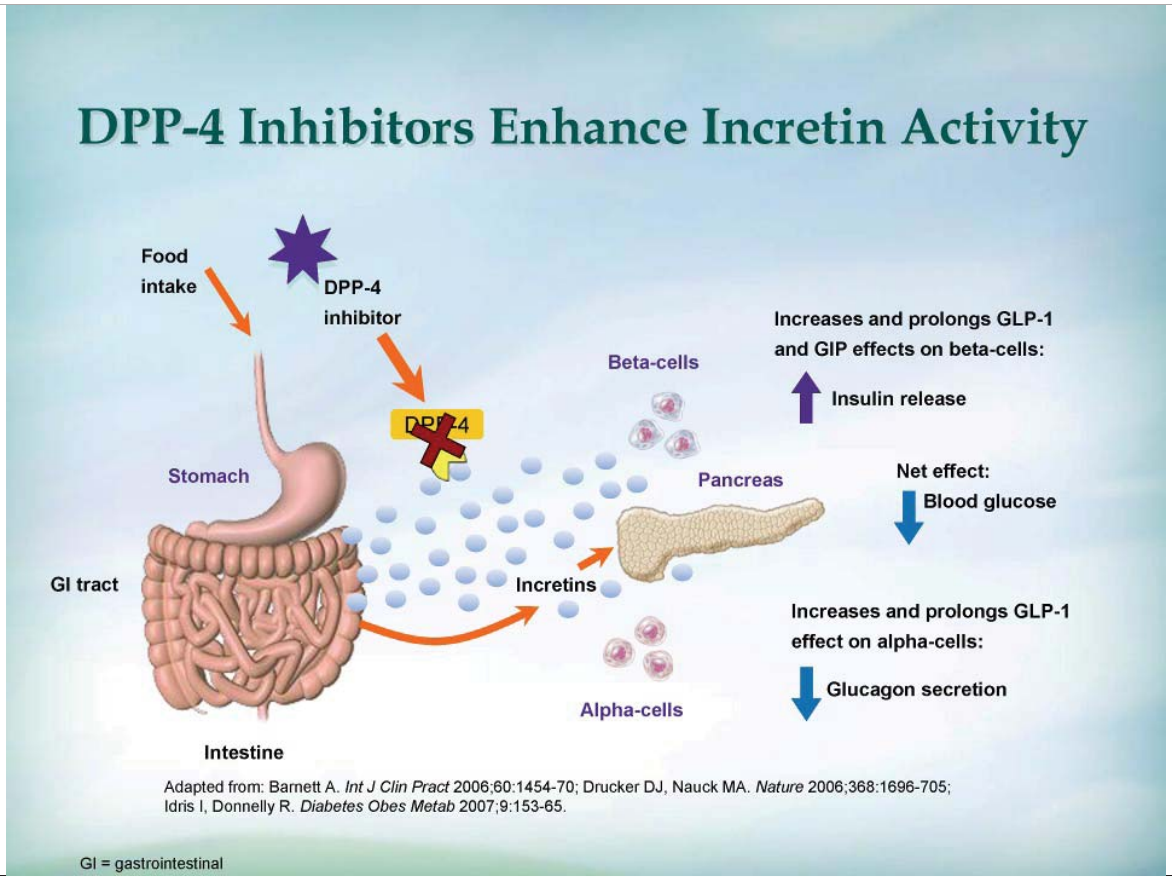
Adapted from: Inzucchi SE, Sherwin RS in: *Cecil Medicine* 2011

Incretins



Adapted from: Kim W *et al. Pharmacol Rev* 2008;60:470-512.

GI = gastrointestinal



Incretin based therapies

Agents that mimic the actions GLP-1

GLP-1 receptor analogs:

- Liraglutide (Victoza)
- Exenatide (Byetta, Bydureon)
- Dulaglutide (Trulicity)
- Semaglutide (Ozempic, Rybelsus)

Agents that limit the degradation of incretins

DPP-4 inhibitors:

- Sitagliptin (Januvia)
- Saxagliptin (Onglyza)
- Linagliptin (Tragenta)
- Alogliptin (Nesina)

GLP-1 receptor agonists

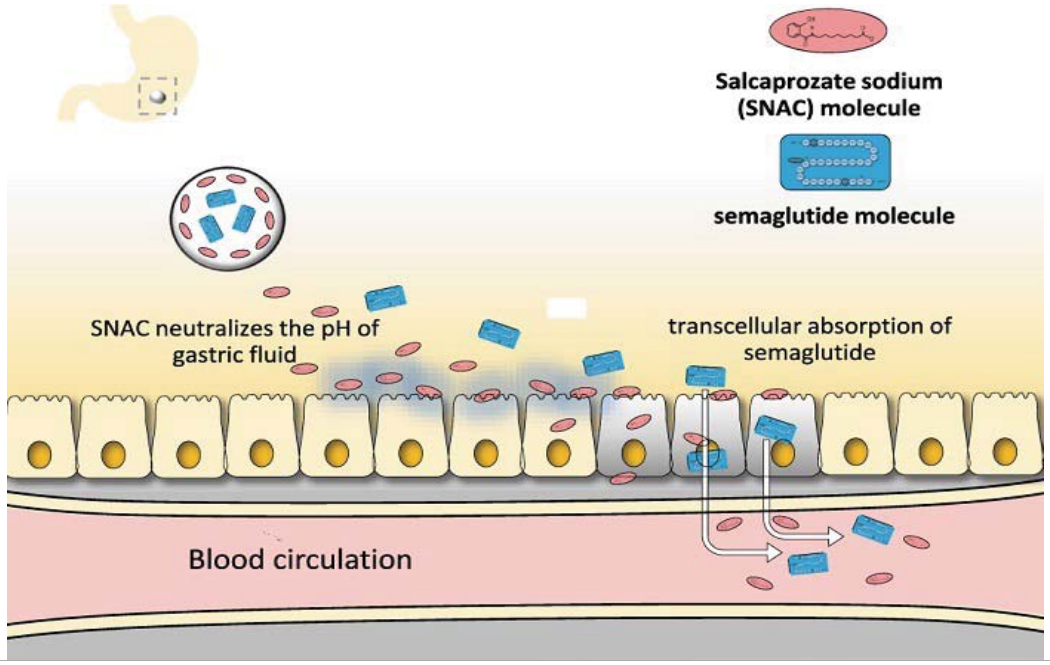
Advantages

- A1C reduction 0.6-1.4%
- Weight loss ~1.1-4.4 kg
- Low risk of hypoglycemia
- Cardiovascular benefit

Disadvantages

- SC injections
- expensive
- GI side effects
- Risk of worsening retinopathy
- Médicament d'exception-RAMQ
- Contraindicated if family history of medullary thyroid cancer or MEN2
- pancreatitis

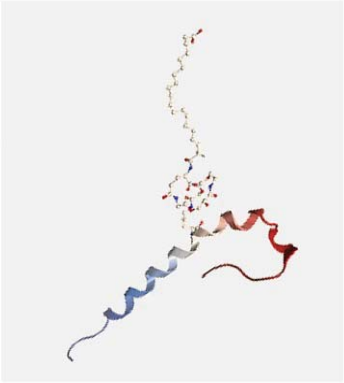
Oral Semaglutide - Rybelsus



Dual GLP-1/GIP agonists

Tirzepatide
Molecular Structure, Activity and PK Characteristics

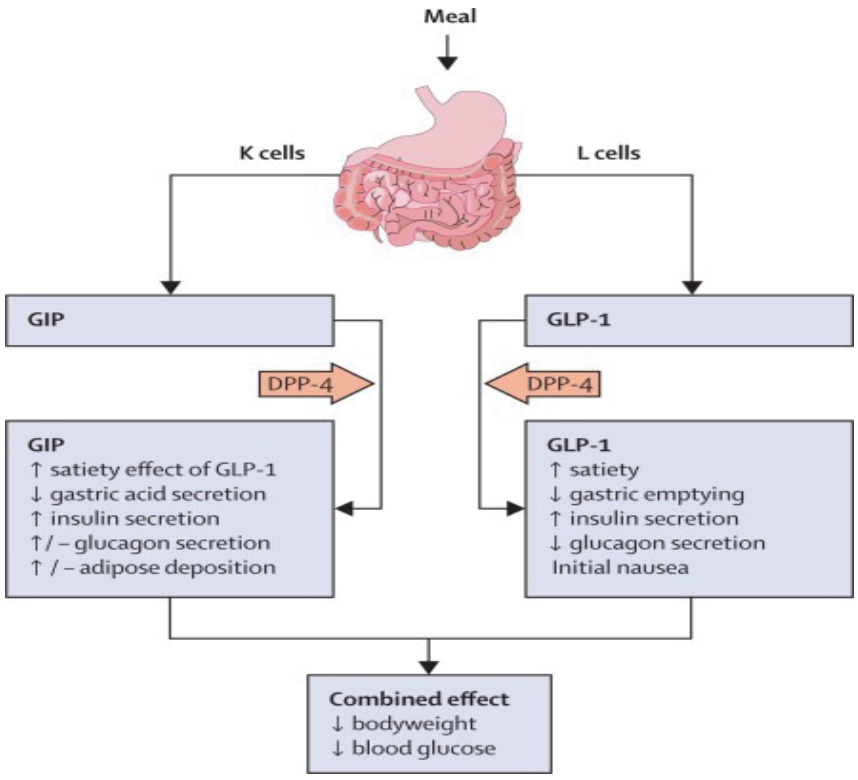
- Tirzepatide (TZP; LY3298176) is a 39 amino acid synthetic peptide with agonist activity at both the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors
- Its structure is based on the GIP sequence and includes a C20 fatty diacid moiety[1]
- Mean half-life is approximately 5 days in man (116.7 h), supporting once-weekly dosing



PK: pharmacokinetic

1. Coskun et al. Mol Metab. 2018;18:3-14

Role of GIP and GLP-1



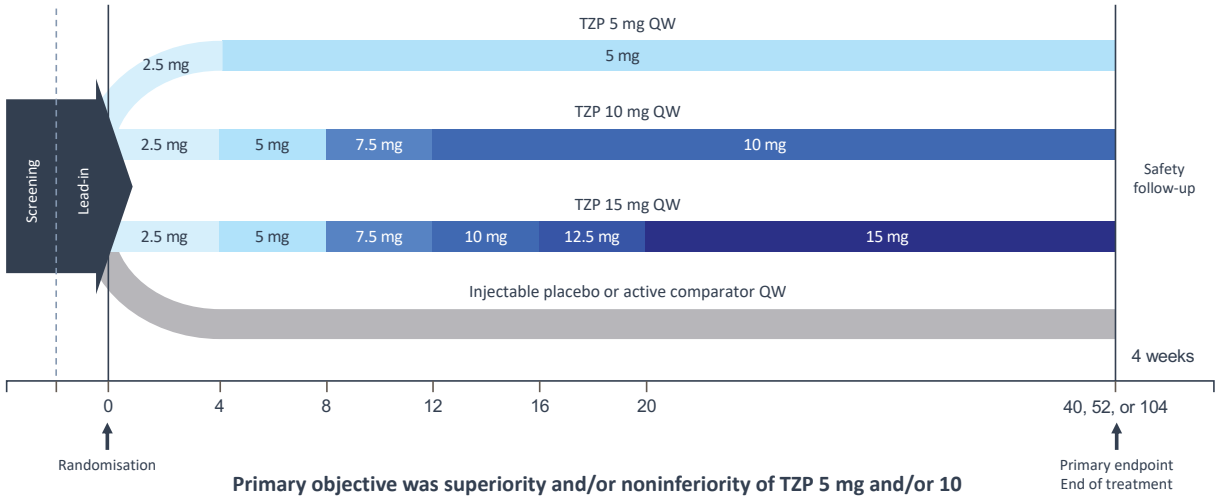
SURPASS Clinical Trial Program

Monotherapy	Combination With OAMs			Combination With Insulin
SURPASS-1 vs placebo[1] (mean T2D duration: 4.7 y)	**SURPASS-2 vs semaglutide[2]** Add-on to metformin (mean T2D duration: 8.6 y)	**SURPASS-3 vs insulin degludec[3]** Add-on to metformin with or without SGLT2i (mean T2D duration: 8.4 y)	**SURPASS-4 vs insulin glargine[4]** Add-on to ≥1 and ≤3 OAMs (metformin, SGLT2i, or SU) (mean T2D duration: 11.8 y)	**SURPASS-5 vs placebo[5]** Add-on to insulin glargine with or without metformin (mean T2D duration: 13.3 y) **SURPASS-6[7] vs insulin lispro (TID)** Add-on to insulin glargine with or without metformin (ongoing)

SURPASS-CVOT vs dulaglutide (ongoing)[6]

OAM = oral antihyperglycaemic medication; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SU = sulphonylurea; TID = thrice daily; T2D = type 2 diabetes.
1. Rosenstock J, et al. *Lancet*. Published online June 26, 2021. 2. Frias JP, et al. *N Engl J Med*. Published online June 25, 2021. 3. Ludvik B, et al. *Lancet*. 2021; In press. 4. Eli Lilly and Company, 2021. Accessed 5 June 2021. https://investor.lilly.com/news-releases/news-release-details/lillys-tirzepatide-achieves-all-primary-and-key-secondary-study 5. Dahl D, et al. Presented at the 81st Scientific Sessions of the ADA. 2021. 6. SURPASS-CVOT. Accessed 1 April 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT04255433 7. SURPASS-6. Accessed 1 April 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT04537923

SURPASS Study Design[1-5]

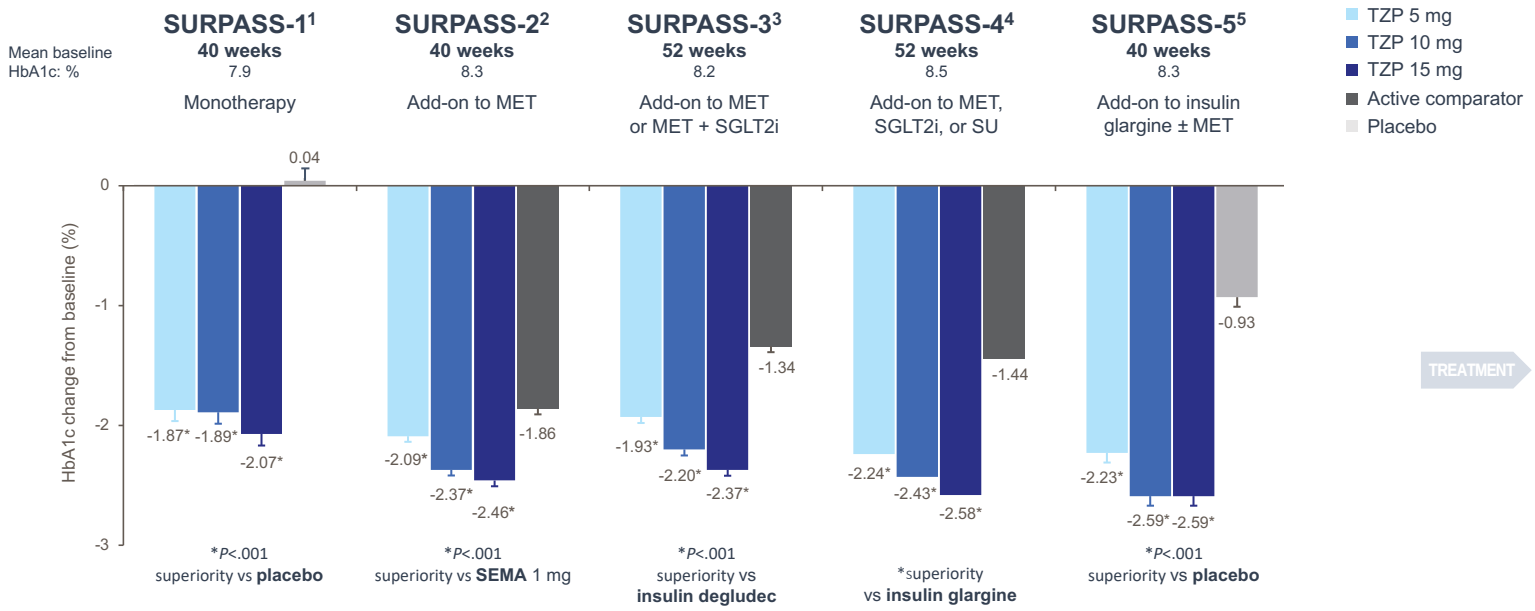


Primary objective was superiority and/or noninferiority of TZP 5 mg and/or 10 mg and/or 15 mg vs placebo or active comparator in mean change in HbA1c from baseline at 40 or 52 weeks.

HbA1c = glycated haemoglobin; QW = once weekly; TZP = tirzepatide.
1. Rosenstock J, et al. Lancet. Published online June 26, 2021. 2. Frias JP, et al. *N Engl J Med*. Published online June 25, 2021. 3. Ludvik B, et al. *Lancet*. 2021; In press. 4. Eli Lilly and Company, 2021. Accessed 5 June 2021. https://investor.lilly.com/news-releases/news-release-details/lillys-tirzepatide-achieves-all-primary-and-key-secondary-study 5. Dahl D, et al. Presented at the 81st Scientific Sessions of the ADA. 2021.

HbA1c Change From Baseline to Primary Endpoint

Efficacy Estimand

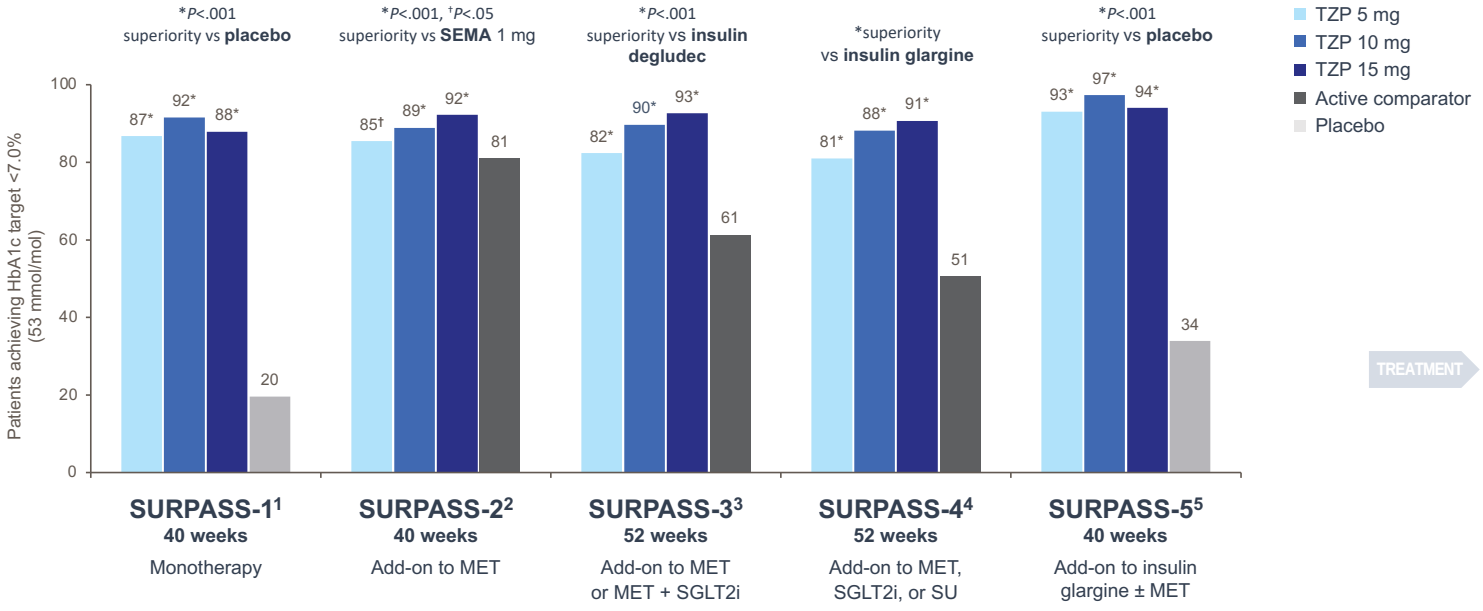


Data are LSM (SE). mITT population (efficacy analysis set). MMRM analysis. Data labels are % HbA1c.
HbA1c = glycated haemoglobin; LSM = least squares mean; MET = metformin; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SEMA = semaglutide; SU = sulphonylurea; TZP = tirzepatide.

1. Rosenstock J, et al. *Lancet*. Published online June 26, 2021. 2. Frias JP, et al. *N Engl J Med*. Published online June 25, 2021. 3. Ludvik B, et al. *Lancet*. 2021; In press. 4. Eli Lilly and Company, 2021. Accessed 5 June 2021. https://investor.lilly.com/news-releases/news-release-details/lillys-tirzepatide-achieves-all-primary-and-key-secondary-study 5. Dahl D, et al. Presented at the 81st Scientific Sessions of the ADA. 2021.

Proportion of Patients Achieving HbA1c <7.0%

Efficacy Estimand

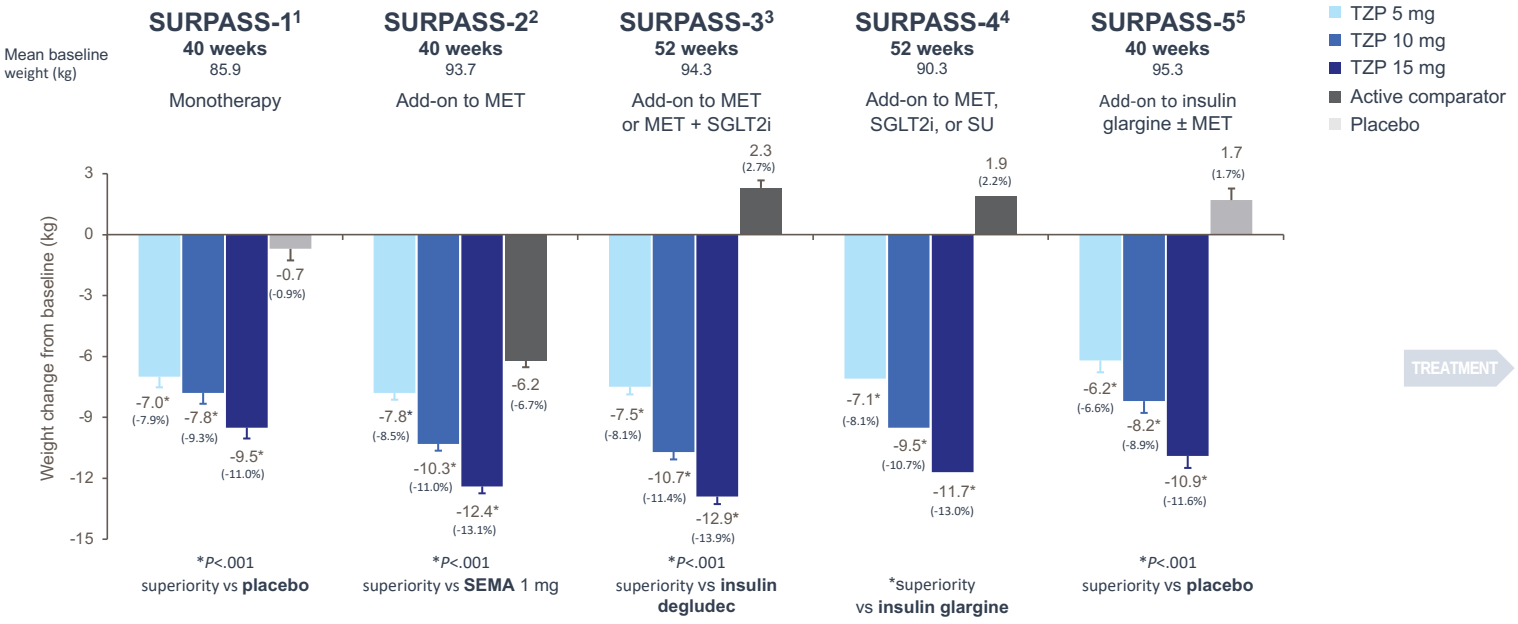


Data are estimated mean; mITT population (efficacy analysis set). Logistic regression.
HbA1c = glycated hemoglobin; MET = metformin; mITT = modified intent-to-treat; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SEMA = semaglutide; SU = sulphonylurea; TZP = tirzepatide.

1. Rosenstock J, et al. *Lancet*. Published online June 26, 2021. 2. Frias JP, et al. *N Engl J Med*. Published online June 25, 2021. 3. Ludvik B, et al. *Lancet*. 2021; In press. 4. Eli Lilly and Company, 2021. Accessed 5 June 2021. https://investor.lilly.com/news-releases/news-release-details/lillys-tirzepatide-achieves-all-primary-and-key-secondary-study 5. Dahl D, et al. Presented at the 81st Scientific Sessions of the ADA. 2021.

Body Weight Change From Baseline to Primary Endpoint

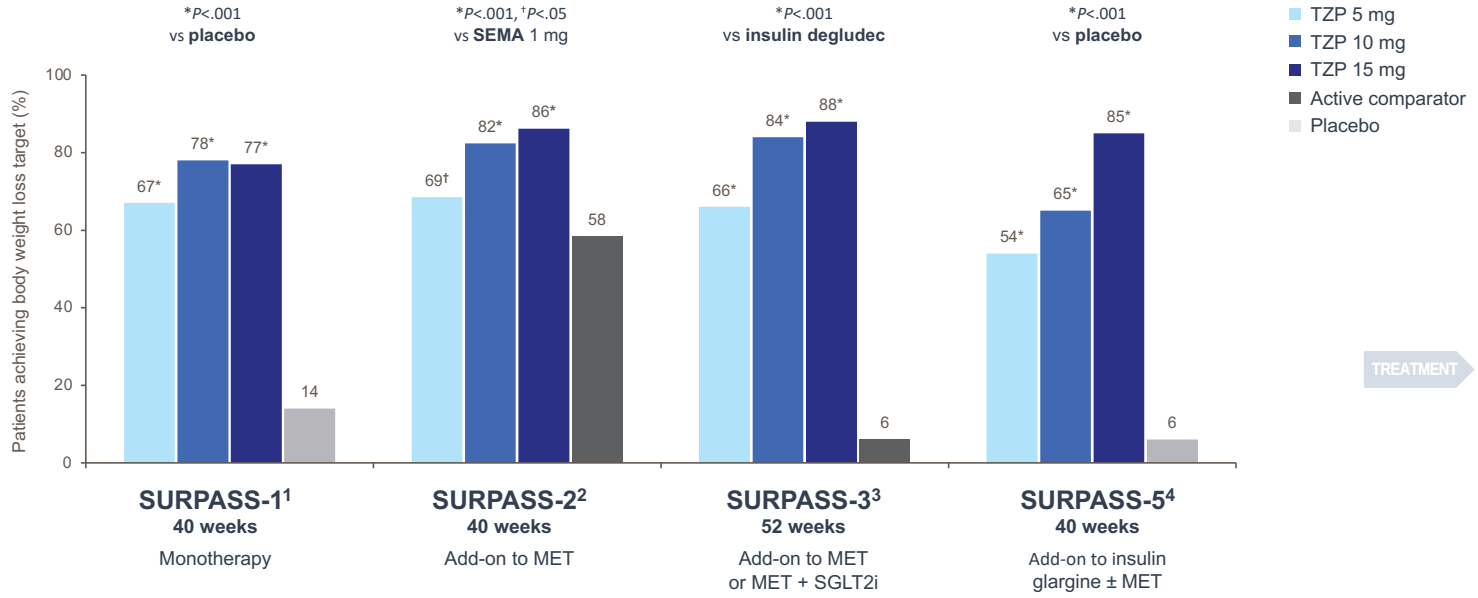
Efficacy Estimand



Data are LSM (SE); mITT population (efficacy analysis set). MMRM analysis.
LSM = least squares mean; MET = metformin; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SEMA = semaglutide; SU = sulphonylurea; TZP = tirzepatide.
1. Rosenstock J, et al. *Lancet*. Published online June 26, 2021. 2. Frias JP, et al. *N Engl J Med*. Published online June 25, 2021. 3. Ludvik B, et al. *Lancet*. 2021; In press. 4. Eli Lilly and Company, 2021. Accessed 5 June 2021. https://investor.lilly.com/news-releases/news-release-details/lillys-tirzepatide-achieves-all-primary-and-key-secondary-study. 5. Dahl D, et al. Presented at the 81st Scientific Sessions of the ADA. 2021.

Proportion of Patients Achieving ≥5% Weight Loss

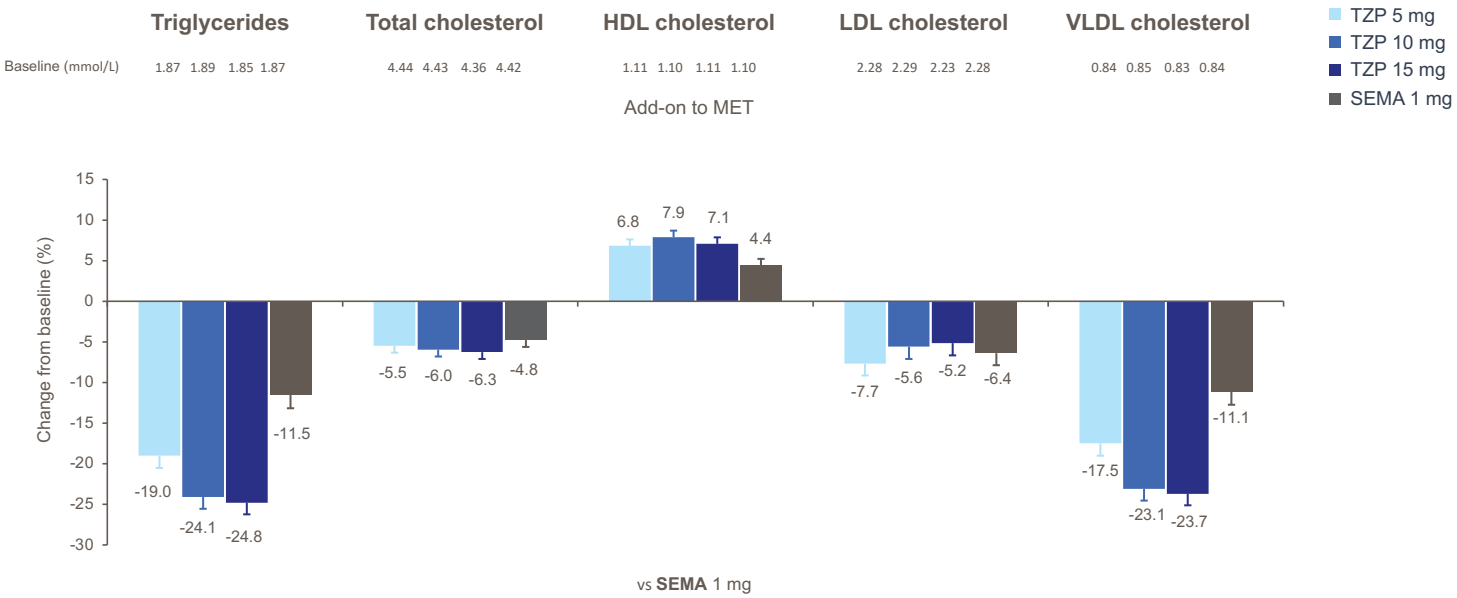
Efficacy Estimand



Data are estimated mean; mITT population (efficacy analysis set). Logistic regression.
MET = metformin; mITT = modified intent-to-treat; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SEMA = semaglutide; TZP = tirzepatide.
1. Rosenstock J, et al. *Lancet*. Published online June 26, 2021. 2. Frias JP, et al. *N Engl J Med*. Published online June 25, 2021. 3. Ludvik B, et al. *Lancet*. 2021; In press. 4. Dahl D, et al. Presented at the 81st Scientific Sessions of the ADA. 2021.

Lipid Profile at 40 Weeks (SURPASS-2)

Efficacy Estimand



Data are estimated percentage means (SE) from MMRM analysis using log transformation; mITT population (efficacy analysis set).
HDL = high-density lipoprotein; LDL = low-density lipoprotein; MET = metformin; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; SEMA = semaglutide; TZP = tirzepatide; VLDL = very-low-density lipoprotein.
Frias JP, et al. *N Engl J Med*. Published online June 25, 2021.

CV Safety Meta-Analysis

- Conducted across the clinical programme once a predefined number of MACE occurred
- Consisted of 116 participants with adjudicated MACE
  - Composite endpoint of death from CV or undetermined causes, MI, stroke and hospitalisation for unstable angina

HR=0.81 (97.85% CI, 0.52 to 1.26)

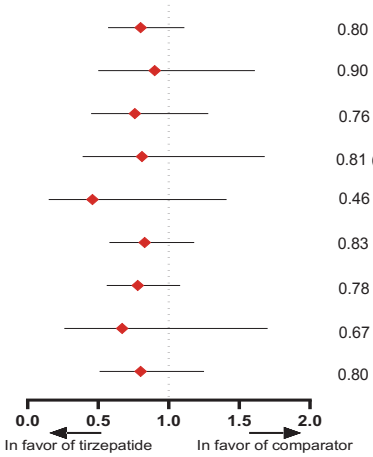
of pooled TZP vs pooled comparators

- The SURPASS clinical trial programme has now met regulatory submission requirements for evaluating CV risk

CV = cardiovascular; HR = hazard ratio; MACE = major adverse cardiovascular events; MI = myocardial infarction; TZP = tirzepatide.
Eli Lilly and Company, 2021. Accessed 5 June 2021. https://investor.lilly.com/news-releases/news-release-details/lillys-tirzepatide-achieves-all-primary-and-key-secondary-study

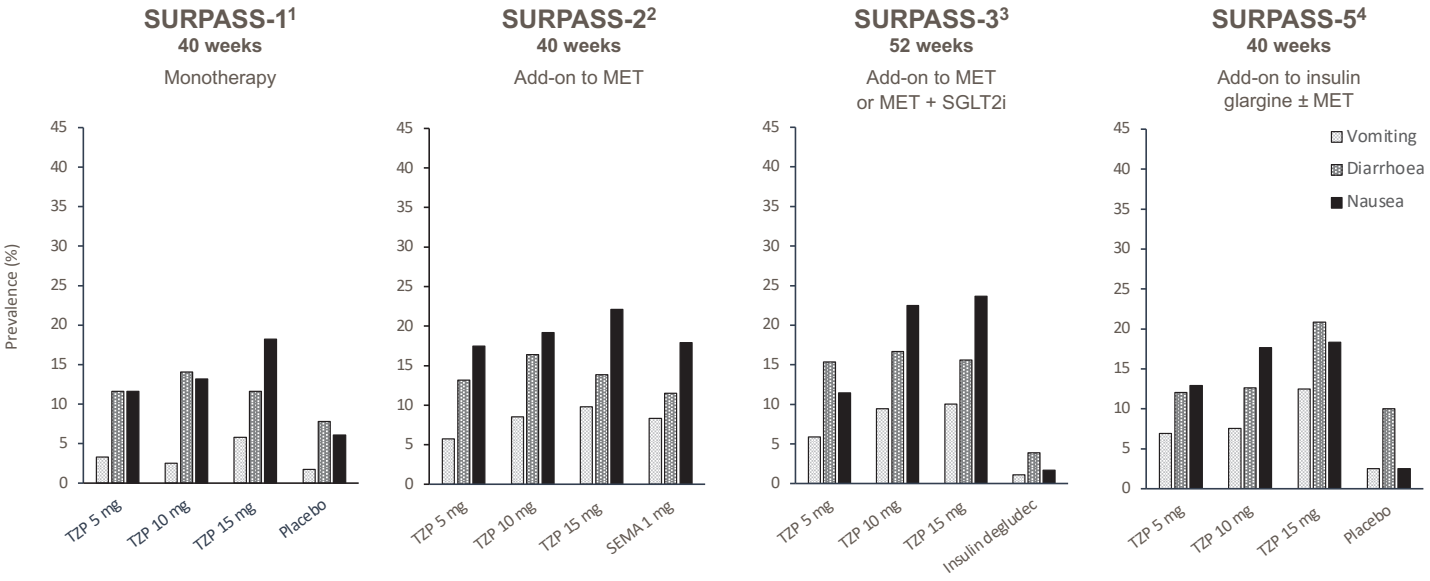
Primary and Secondary Cardiovascular Outcomes Confirmed by Centrally Blinded Adjudication

	All Tirzepatide N=4887 n (n/100 Person-Years[a])	All Comparator N=2328 n (n/100 Person-Years[a])	HR With 95% CI	HR (95% CI)	*P* Value
Composite MACE-4	72 (1.35)	70 (1.61)		0.80 (0.57, 1.11)	0.183
Death due to cardiovascular cause[b]	25 (0.46)	22 (0.43)		0.90 (0.50, 1.61)	
Myocardial infarction	30 (0.56)	30 (0.71)		0.76 (0.45, 1.28)	
Stroke	15 (0.27)	15 (0.35)		0.81 (0.39, 1.68)	
Hospitalization for unstable angina	5 (0.09)	9 (0.20)		0.46 (0.15, 1.41)	
Composite MACE-3[c]	67 (1.25)	62 (1.42)		0.83 (0.58, 1.18)	0.306
Composite MACE-3 or hospitalization for heart failure	74 (1.39)	71 (1.71)		0.78 (0.56, 1.08)	0.137
Hospitalization for heart failure	10 (0.19)	9 (0.29)		0.67 (0.26, 1.70)	
All-cause death	41 (0.76)	39 (0.86)		0.80 (0.51, 1.25)	



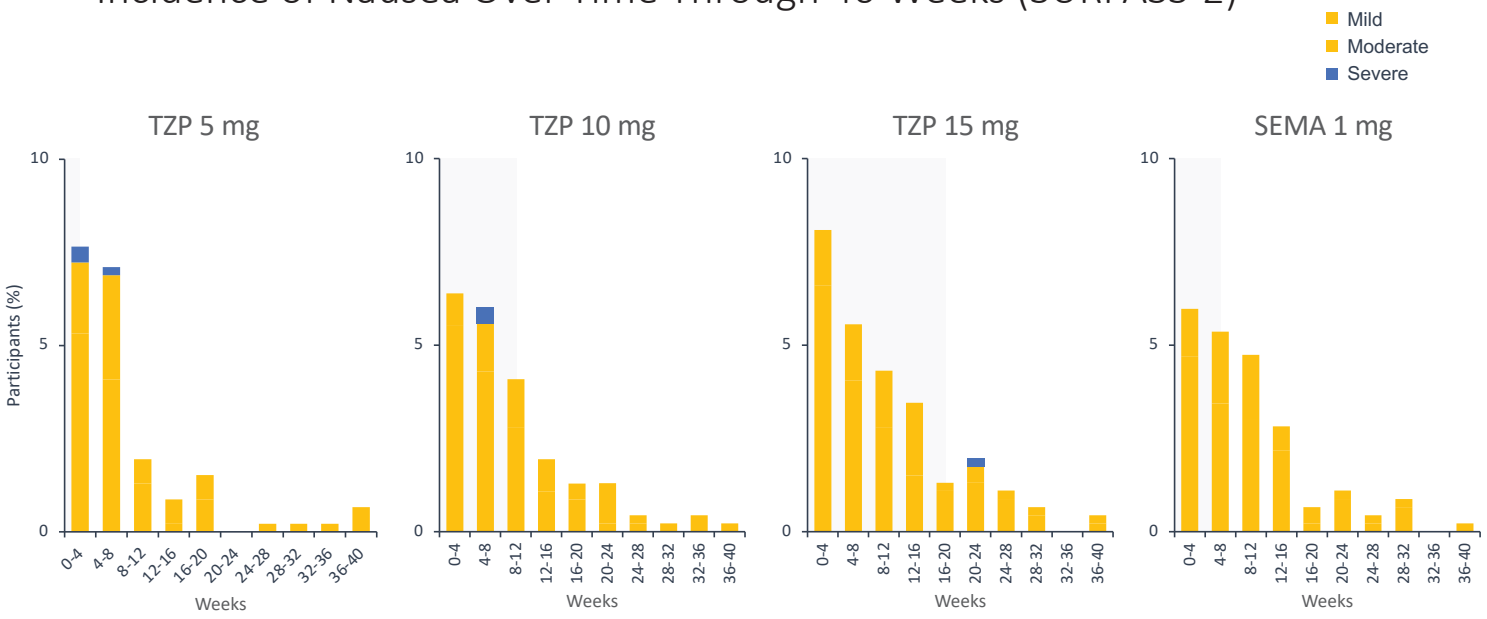
[a]Strata size adjusted estimate. Strata are defined as trial-level cardiovascular risk (SURPASS-4 forms one stratum, and all other trials form one stratum). [b]Death due to cardiovascular cause includes adjudication-confirmed deaths due to a cardiovascular or undetermined cause. [c]MACE-3 includes death due to cardiovascular or undetermined cause, myocardial infarction, or stroke.
Note: *P* values were based on the Wald Chi-square test. Data are point estimate of HR (illustrated by the diamond symbol) and range of 2-sided 95% CI of the HR.
HR=Hazard Ratio; CI=Confidence Interval; MACE=Major Adverse Cardiovascular Event.
Sattar N, et al. *Nat Med.* 2022; (Ahead of Print).

Prevalence of Vomiting, Diarrhoea, and Nausea



Data are percentage of TEAE with ≥5% frequency in any arm; mITT population (safety analysis set). Note: Patients may be counted in more than 1 category.
MET = metformin; mITT = modified intent-to-treat; SEMA = semaglutide; SGLT2i = sodium-glucose co-transporter-2 inhibitor; TEAE = treatment-emergent adverse event; TZP = tirzepatide.
1. Rosenstock J, et al. Presented at the 81st Scientific Sessions of the ADA. 2021. 2. Frias JP, et al. Presented at the 81st Scientific Sessions of the ADA. 2021. 3. Ludvik B, et al. *Lancet*. 2021; In press. 4. Dahl D, et al. Presented at the 81st Scientific Sessions of the ADA. 2021.

Incidence of Nausea Over Time Through 40 Weeks (SURPASS-2)

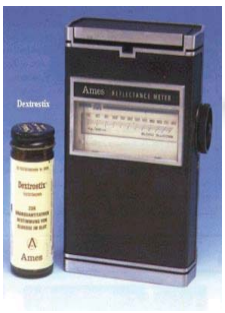


Data are percentage of participants who reported a new event relative to participants at risk during a time interval; mITT population (safety analysis set). Shaded areas indicate the period of time before reaching the maintenance dose of the study treatments. Incidence refers to the proportion of participants who have a new event during a time interval.
mITT = modified intent-to-treat; SEMA = semaglutide; TZP = tirzepatide.
Frias JP, et al. *N Engl J Med*. Published online June 25, 2021.

Conclusions: Tirzepatide

- Novel dual GIP/GLP-1 receptor agonist therapy
- Subcutaneous injection once weekly
- A1C reduction of 2-2.6%
- Weight loss of 6-13 kg
- Well tolerated: nausea and vomiting comparable to semaglutide
- Cardiovascular benefit??

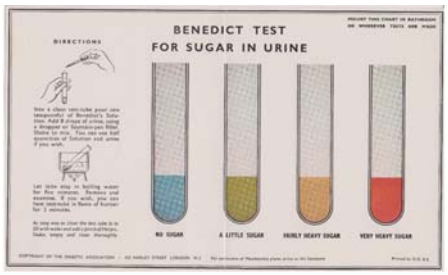
Evolution of Glucose Testing



1908

1970's

2000's

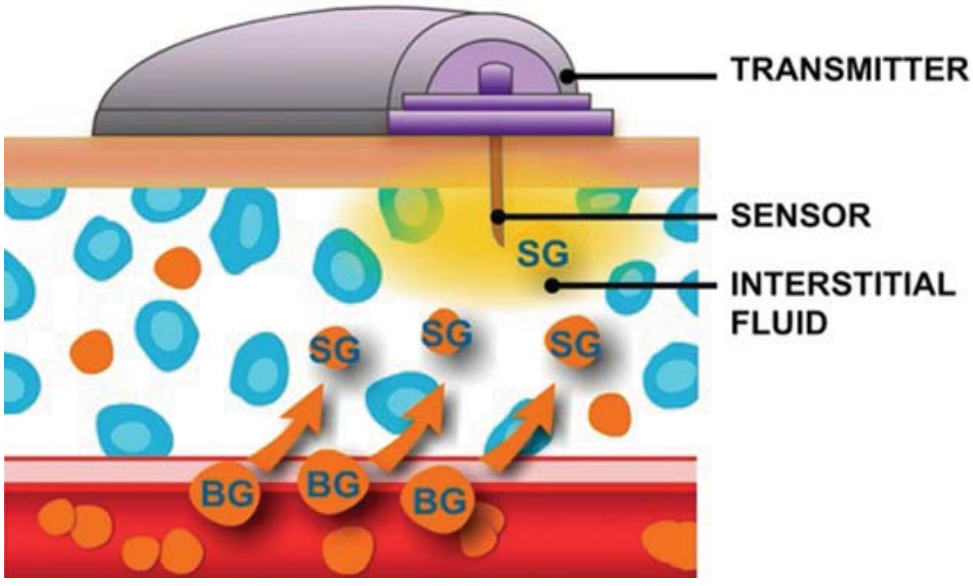


1980's

1. Clarke S, Foster J. *Br J Biomed Sci*. 2012;69:83-93.

Continuous glucose monitoring systems

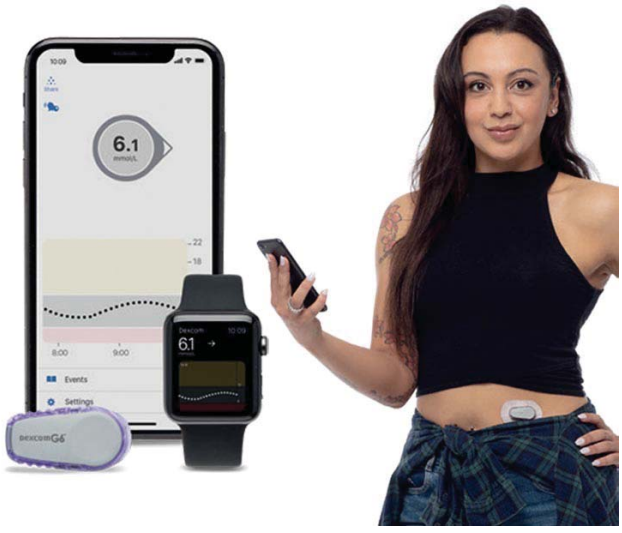
3 components:
1.Sensor
2.Transmitter
3.Receiver



Freestyle libre 1 and 2

CGM by intermittent scanning
ex. Freestyle Libre

Dexcom G6



CGM in real time
ex. Dexcom G6

NEW GLUCOSE MONITORING TERMS[1]

CBG	isCGM	rtCGM
Measures glucose in capillary blood using fingersticks	Measures interstitial fluid glucose via intermittent scan of sensing device	Measures interstitial glucose via sensing device that is continuously transmitting data to device with real time display for viewing at any time

CBG, capillary blood glucose; isCGM, intermittently scanned continuous glucose monitoring, rtCGM, real-time continuous glucose monitoring.

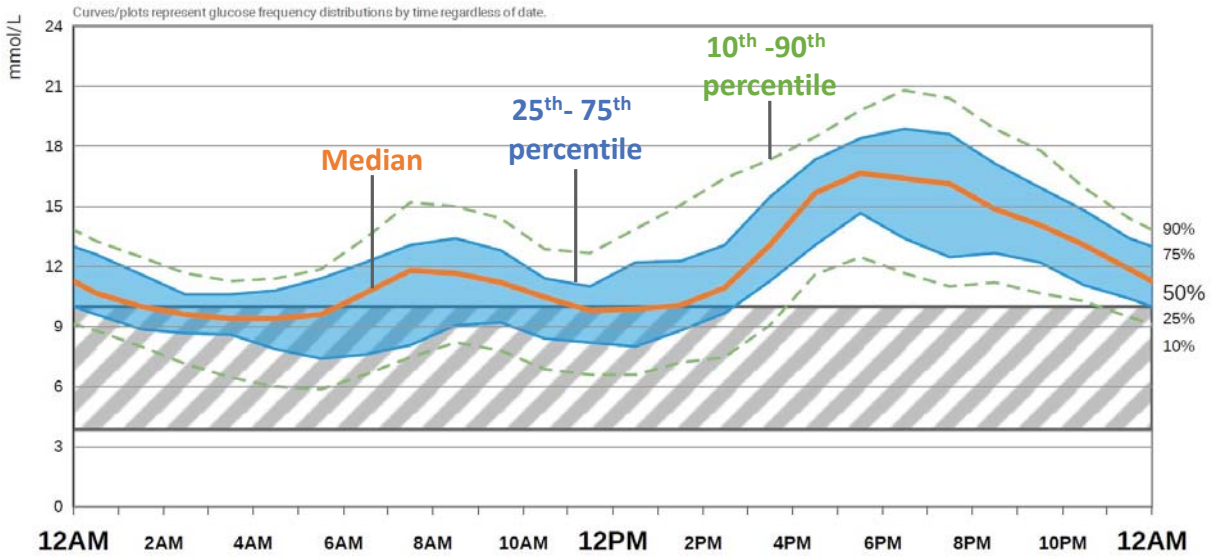
[1] Cheng A, Feig DS, Ho J and Siemens R. Can J Diabetes. 2021; 45: 580-587.

What we've seen in the office….

Mei
HbA1c = 7,0 %

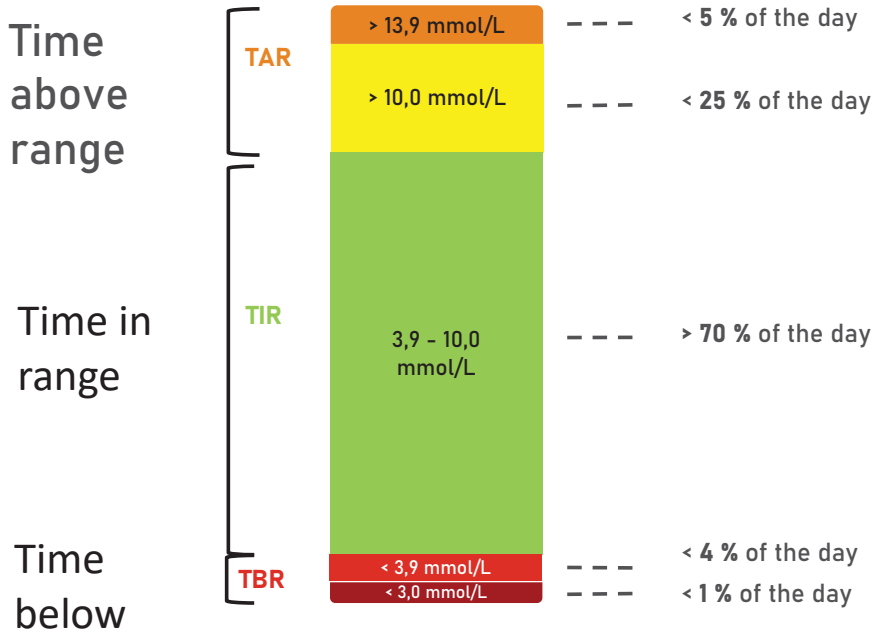
HbA1c : hémoglobine glyquée
Les images ne sont utilisées qu'à des fins d'illustration seulement.

AGP-Ambulatory Glucose Profile



[1] Dunn TC et al. *J Diabetes Sci Technol* 2014;8(4):720-730..

What are the targets?



[1]Battelino T et al. *Diabetes Care*. 2019; 42(8): 1593-1603. Cheng A, Feig DS, Ho J and Siemens R. Can J Diabetes. 2021;45: 580-587.

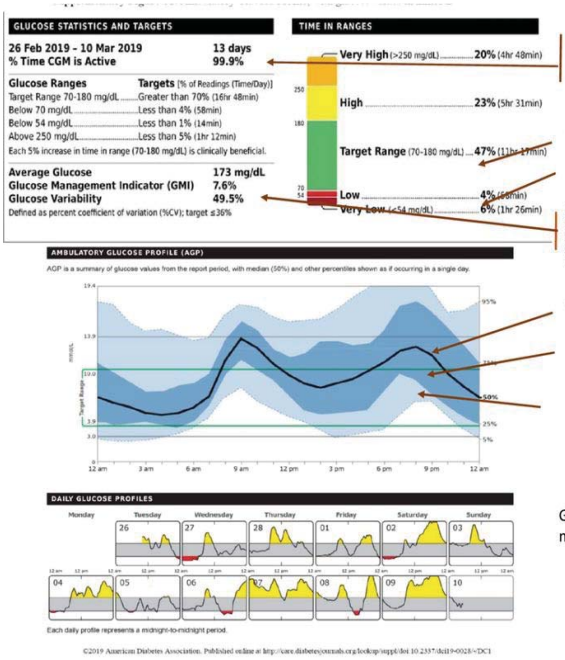
Standardized CGM metrics for clinical care[1]

	T1D & T2D		Older/High-Risk T1D & T2D	
Time above range **TAR**	> 13.9 mmol/L	< 5% of day	> 13.9 mmol/L	< 10 % of day
	> 10.0 mmol/L	< 25% of day	> 10.0 mmol/L	< 50% of day
Time in range **TIR**	3.9 - 10.0 mmol/L	> 70% of day	3.9 - 10.0 mmol/L	> 50% of day
Time below range **TBR**	< 3.9 mmol/L	< 4 % of day		
	< 3.0 mmol/L	< 1 % of day	<3.9 mmol/L	< 1 % of day

Other key metrics	Targets
Days CGM worn	14+
% Time CGM active	>70%
GMI or eA1C Estimate of current A1C	
CV Measure of glycemic variability	≤ 36%

A1C, hemoglobin A1c; CGM, continuous glucose monitoring; CV, coefficient of variation; GMI, glucose management indicator; T1D, type 1 diabetes; T2D, type 2 diabetes.
[1]Battelino T et al. *Diabetes Care*. 2019; 42(8): 1593-1603.

AGP (Ambulatory Glucose Profile)



Ambulatory Glucose profile (AGP) report is displayed for 14 days of sensor wear. It correlates well to 3 months of *CGM data
CGM is active 99.9%% of time. Recommendation is for min 70% usage (10 days) for reliable data

Time in range (TIR)- aim is to slowly increase time spent in range. TIR (3.9-10mmol/l) of 70% correlates to HbA1c of 53 mmol/mol
Aim for low (<3.9 mmol/l) to be limited to < 5% and very low (<3.0mmol/l) to be <1%

Glucose Management Indicator (GMI)- Provides with estimated HbA1c

Glucose variability (GV)- refers to how much the glucose readings varies from mean or median glucose. Low GV indicates stable glucose profile

Ambulatory glucose profile: The **solid line** is the median or 50% line; half of all glucose values are above and half are below this value.
The 25th and 75th percentile curves shaded in **dark blue** represent the interquartile range or 50% of all values and are a good visual indicator of the degree of GV.
The dashed outer lines (the 10th to 90th percentile curves) in **light blue** indicate that only 10% of glucose readings were above or below these value

Graph showing daily data. Each daily profile represents midnight to midnight data

Astha Soni et al. Arch Dis Child Educ Pract Ed
doi:10.1136/archdischild-2020-321190

Simple AGP report evaluation

What do the NUMBERS tell you?

Other key metrics	Targets
Days CGM worn	14+
% Time CGM active	>70%
GMI or eA1C Estimate of current A1C	
CV Measure of glycemic variability	≤ 36%

CGM, continuous glucose monitoring; GMI, glucose management indicator; eA1C, estimated glycated hemoglobin; CV, coefficient of variation.

Cheng A et al. *Can J Diabetes.* 2021; 45: 580-587.
Battelino T et al. *Diabetes Care*. 2019; 42(8): 1593-1603.

CLARITY images provided for illustration purposes only.

Easy access to glucose data on cloud

Légende
Bluetooth
Internet

Images utilisées uniquement à des fins d'illustration.

Conclusions: continuous glucose monitoring

- Indicated for patients with type 1 and 2 diabetes on multiple doses of insulin

- Decreases A1C
- Decreases severe hypoglycemia
- Increases time in range

Alice Y.Y. Cheng et al. **Blood Glucose Monitoring in Adults and Children with Diabetes: Update 2021**

Thank you for your attention!

Questions?