Congresso Regionale AMD - SID Abruzzo/Molise

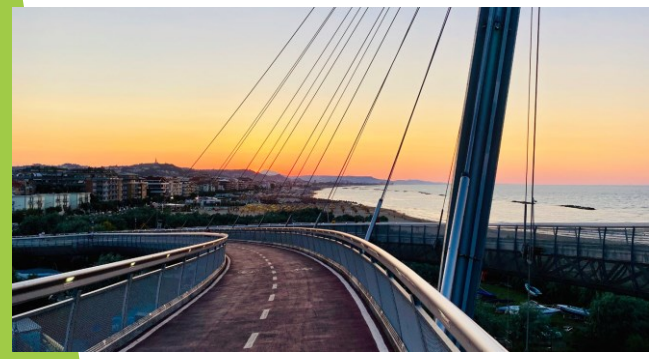
Chieti, 12 novembre 2022

LE FRONTIERE DELLA TECNOLOGIA E DELLA FARMACOLOGIA NELLA GESTIONE DEL DIABETE MELLITO TIPO 2

FIORE PELLICCIONE
fiore.pelliccione@gmail.com

ASL 2 Lanciano-Vasto-Chieti

U.O.C. Medicina Interna
Servizio di Diabetologia
Ospedale "F. Renzetti" - Lanciano - CH



7. Diabetes Technology: *Standards of Medical Care in Diabetes—2022*

*American Diabetes Association Professional Practice Committee**

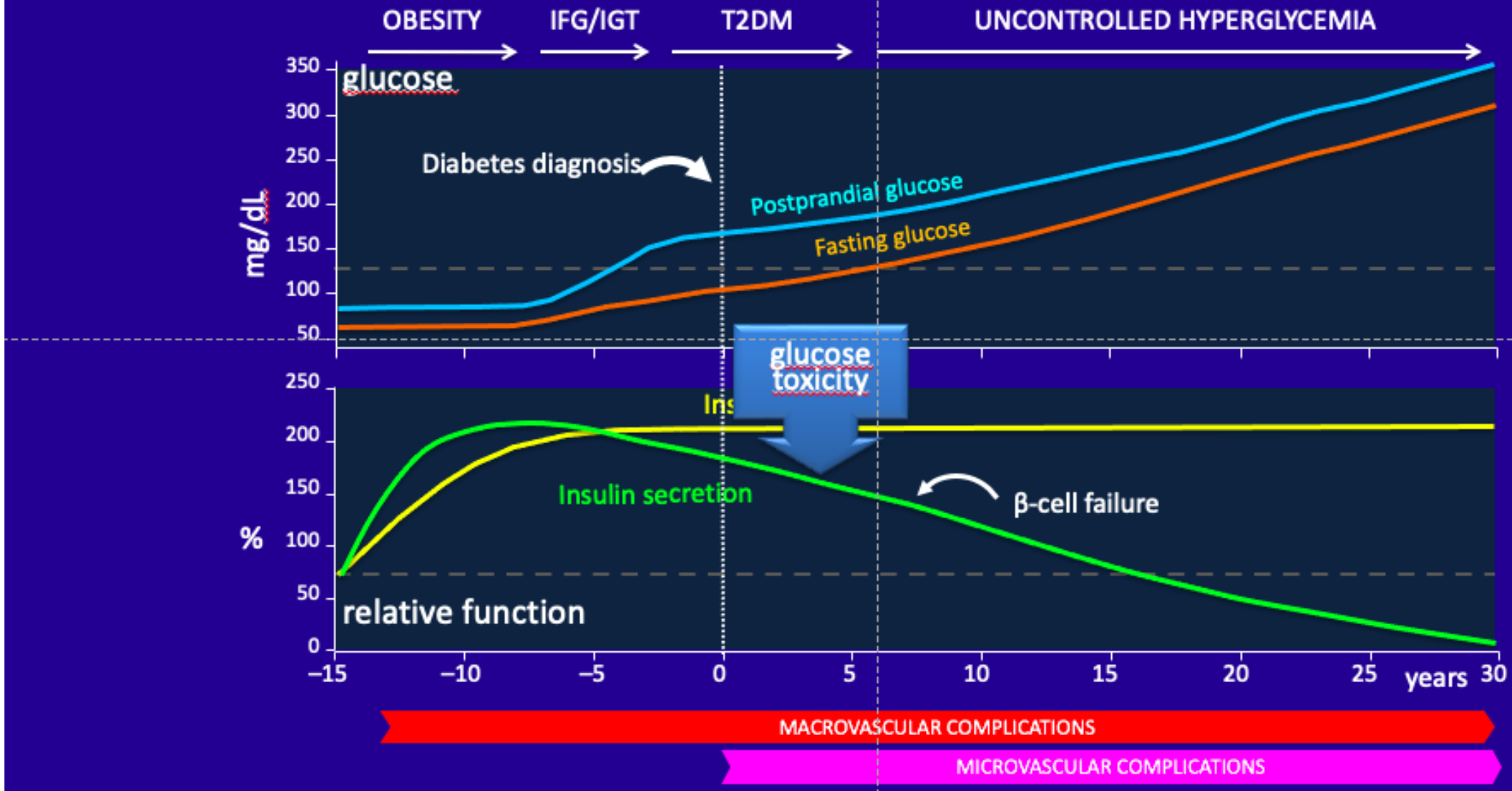
Diabetes Care 2022;45(Suppl. 1):S97–S112 | https://doi.org/10.2337/dc22-S007

Diabetes technology → describe the hardware, devices, and software that people with diabetes use to help manage their condition, from lifestyle to blood glucose levels/insulin delivery.

T1D

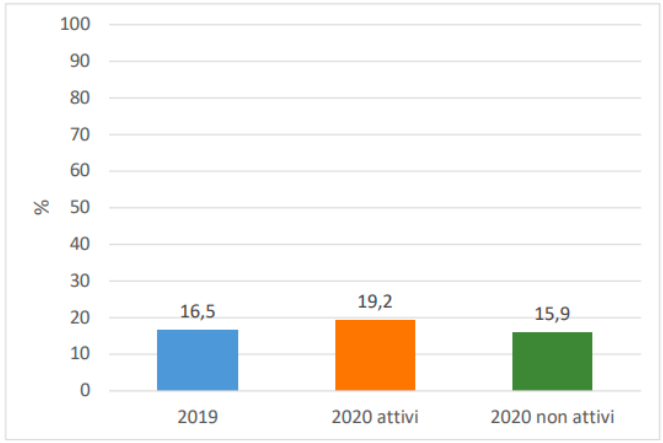
T2D

Natural history of type 2 diabetes



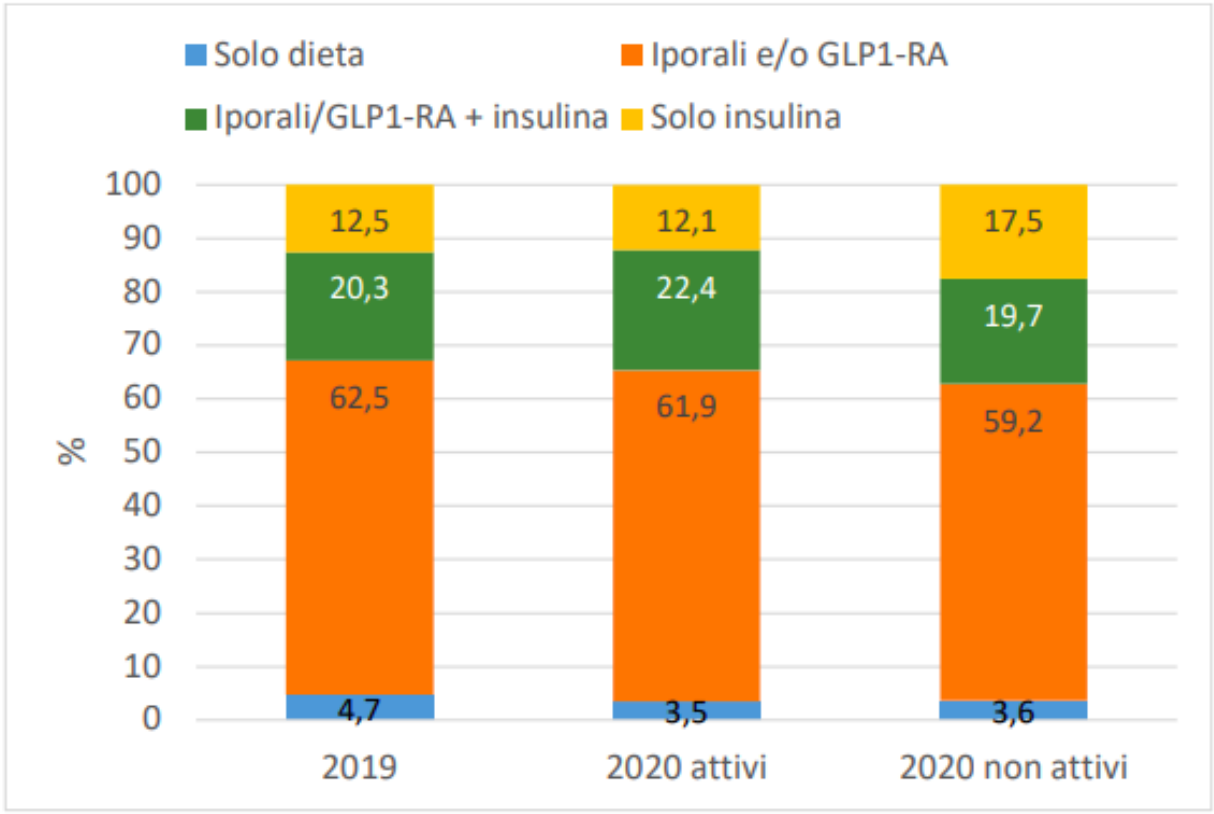
Bailey T. The AmJMedicine 126:S10, 2013

Soggetti con HbA1c ≥9,0% nonostante il trattamento con insulina (%)



Annali AMD 2021

Distribuzione dei pazienti per intensità di trattamento ipoglicemizzante nel DM2 (%)



SISTEMI AVANZATI DI MONITORAGGIO DEL GLUCOSIO

						
Età di utilizzo	> 4 anni	> 4 anni	> 2 anni	nessun limite	> 18 anni	> 6 anni
Rt-CGM o I-CGM (FGM)	FGM	FGM	Rt-CGM	Rt-CGM	Rt-CGM	Rt-CGM
Piccola chirurgia	NO	NO	NO	NO	SI	NO
Sede	braccia	braccia	addome / braccia (>17 anni)	braccia / addome	braccia	addome
Durata del sensore	14 giorni	14 giorni	10 giorni	7 giorni	180 giorni	14 giorni
Allarmi /avvisi	NO	SI (soglia)	SI (soglia, predittivo IPO)	SI (soglia, predittivi)	SI (soglia, predittivi)	SI (soglia, predittivi)
Calibrazioni	NO	NO	NO	2 /die	2/die	1/die
Connessione con CSII	NO	NO	SI	SI	NO	NO

FGM vs SMBG IN T2M

- 224 T2D in terapia insulinica (HbA1c media 8.8%)
- Randomizzati SMBG o FGM per 6 mesi
- Riduzione NS HbA1c nei 2 gruppi overall
- **Riduzione significativa HbA1c con FGM nel sottogruppo <65 aa.**
- **Tempo in ipoglicemia (<70 mg/dl) ↓significativamente in FGM (- 1.01 h/notte) nelle ore notturne (-43%)**
- Estensione open label a 12 mesi dello studio → confermata ↓ **significativa riduzione del tempo in ipoglicemia, specie notturna**

Diabetes Ther (2017) 8:55–73
DOI 10.1007/s13300-016-0223-6

CrossMark

ORIGINAL RESEARCH

REPLACE STUDY

Flash Glucose-Sensing Technology as a Replacement for Blood Glucose Monitoring for the Management of Insulin-Treated Type 2 Diabetes: a Multicenter, Open-Label Randomized Controlled Trial

Thomas Haak · Hélène Hanaire · Ramzi Ajjan · Norbert Hermanns ·

FGM vs SBMG IN T2M

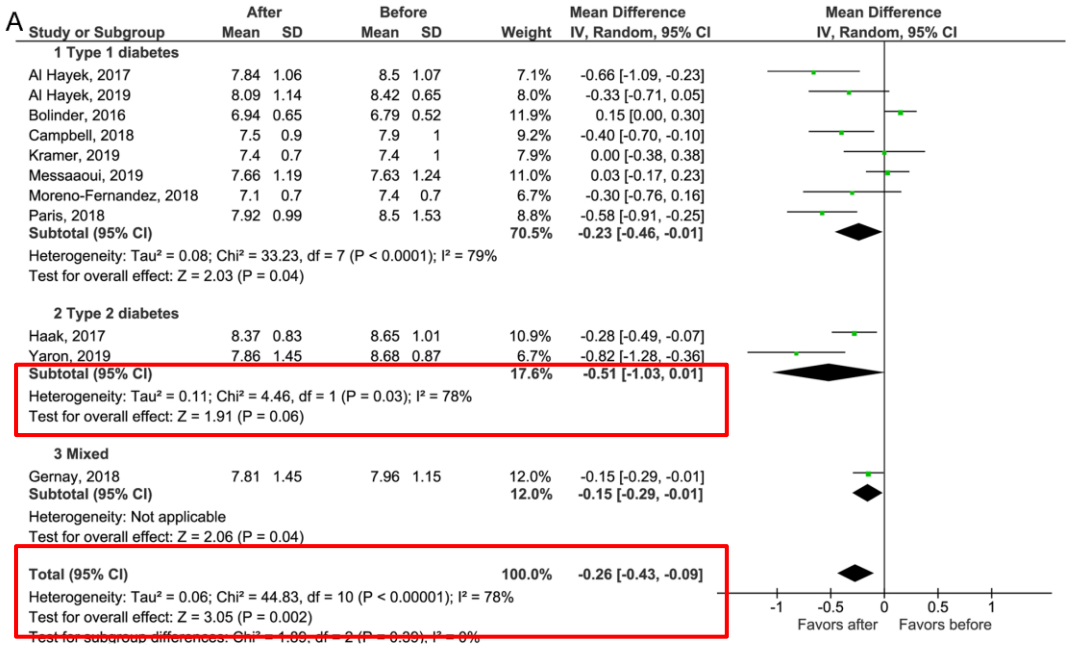
- 12 studies (3 RCT) follow-up > 8 weeks
- 2173 patients (T1D/T2D) on prandial insulin, MDI OR CSII
- Pre/Post outcomes: HbA1c, TIR, TAR (>180), TBR (<70 mg/dL), frequency of hypos, TDD, patient-reported outcomes, adverse events, and discontinuation rate.
- Comparison with SMBG

BMJ Open Diabetes Research & Care

2020

Efficacy and safety of flash glucose monitoring in patients with type 1 and type 2 diabetes: a systematic review and meta-analysis

Marco Castellana, Claudia Parisi, Sergio Di Molfetta, Ludovico Di Gioia, Annalisa Natalicchio, Sebastio Perrini, Angelo Cignarelli, Luigi Laviola, Francesco Giorgino



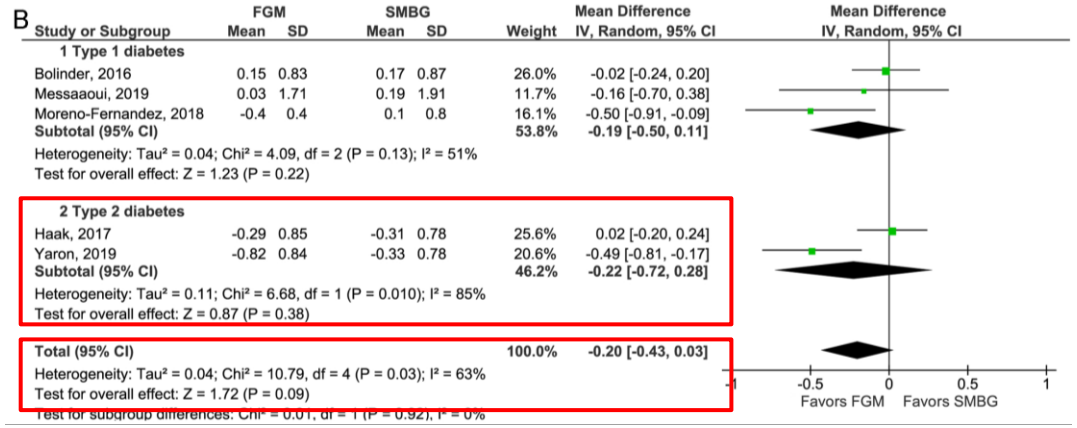


Table 2 Meta-analysis for changes in other outcomes from baseline to the last available follow-up

Parameter	Number of patients (number of studies)	Estimate (95% CI)*	I^2 (%)	P value
Changes in patients using FGM				
Time in range (70–180 mg/dL) (hours/day)	343 (3)	0.55 (–0.17 to 1.26)	48	0.14
Time above 180 mg/dL (hours/day)	343 (3)	0.19 (–0.90 to 1.29)	73	0.73
Time below 70 mg/dL (hours/day)	621 (4)	–0.60 (–1.18 to –0.03)	90	0.04
Hypoglycemic events (n/day)	597 (7)	–0.04 (–0.23 to 0.15)	91	0.67
SMBG measurements (n/day)	401 (5)	–4.55 (–5.74 to –3.35)	95	<0.001
Total daily insulin dose (IU/day)	517 (6)	–1.22 (–4.29 to 1.86)	0	0.44
Differences in changes in patients using FGM versus patients using SMBG				
SMBG measurements (n/day)	832 (4)	–3.76 (–4.79 to –2.72)	86	<0.001
Total daily insulin dose (IU/day)	498 (3)	0.23 (–1.34 to 1.80)	0	0.77
Discontinuation	564 (3)	0.42 (0.25 to 0.71)	0	0.001

*Data are expressed as relative risk for discontinuation and as weighted mean differences for the other outcomes.
FGM, flash glucose monitoring; SMBG, self-monitoring of blood glucose.

Diabetes Obes Metab. 2021 August 01; 23(8): 1722–1732. doi:10.1111/dom.14418.

Technology in the management of type 2 diabetes – present status and future prospects

Aldeen Daly, **Roman Hovorka**

[1]Wellcome Trust-MRC Institute of Metabolic Science, University of Cambridge, Cambridge, United Kingdom

FGM IN T2M

rt-CGM vs SBMG IN T2D

Received: 24 April 2019 | Revised: 4 July 2019 | Accepted: 22 July 2019
DOI: 10.1111/dom.13845

ORIGINAL ARTICLE

WILEY

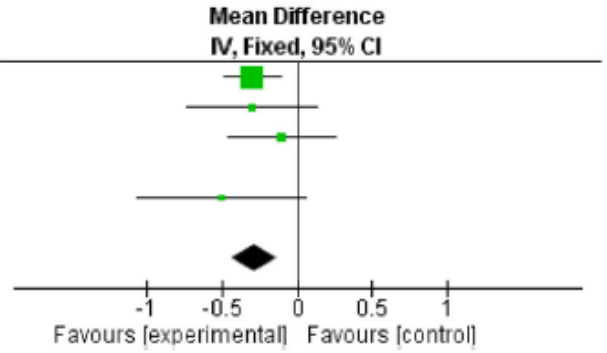
Impact of technology on glycaemic control in type 2 diabetes: A meta-analysis of randomized trials on continuous glucose monitoring and continuous subcutaneous insulin infusion

Ilaria Dicembrini MD[1,2] | Edoardo Mannucci MD[1,2] | Matteo Monami MD[1] |

(B)

Study or Subgroup	CGM Mean	CGM SD	CGM Total	SMBG Mean	SMBG SD	SMBG Total	Weight	Mean Difference IV, Fixed, 95% CI
Beck 2017	7.7	0.6	79	8	0.6	79	63.5%	-0.30 [-0.49, -0.11]
Erhrardt 2011	7.4	1	50	7.7	1.2	50	11.9%	-0.30 [-0.73, 0.13]
Ilany 2018	8.4	1	60	8.5	1	61	17.5%	-0.10 [-0.46, 0.26]
Tang 2014	7.9	1.3	0	0	0	0		Not estimable
Tildesley 2013	7.5	0.7	35	8	1.3	25	7.1%	-0.50 [-1.06, 0.06]
Total (95% CI)			**224**			**215**	**100.0%**	**-0.28 [-0.43, -0.13]**

Heterogeneity: Chi² = 1.63, df = 3 (P = 0.65); I^2 = 0%
Test for overall effect: Z = 3.67 (P = 0.0002)



- Severe hypoglycaemia(3 RCT) → NS
- Nonsevere hypoglycaemia (different definitions – 4 RCT) → NS
- Data on nocturnal hypoglycaemia → not reported
- Quality of life (2 RCT) → NS

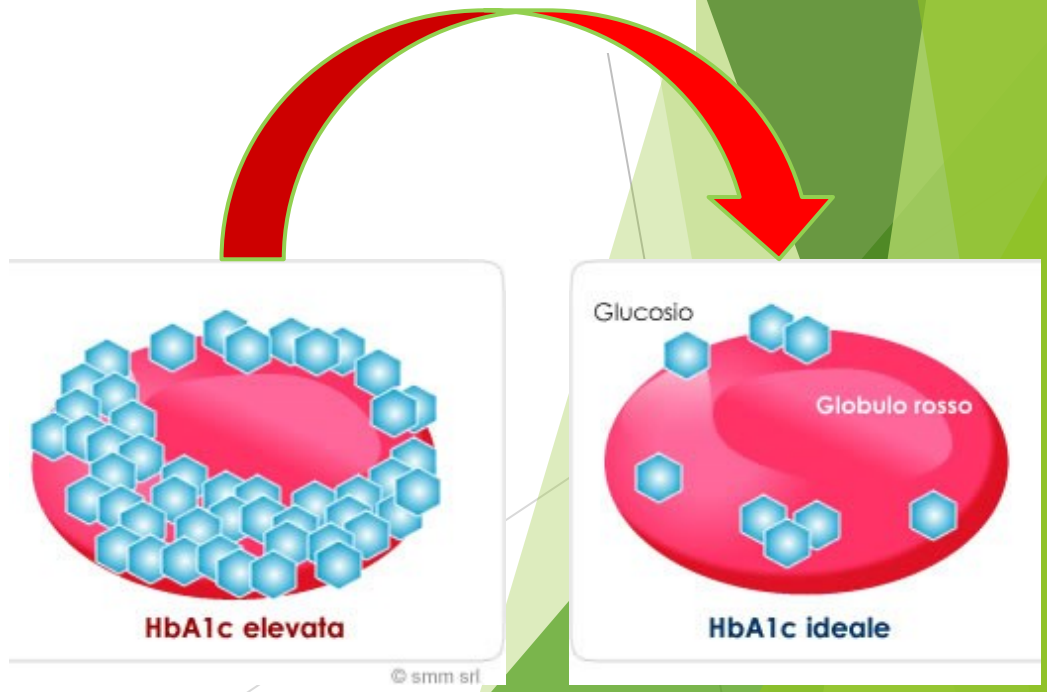
Diabetes Obes Metab. 2021 August 01; 23(8): 1722–1732. doi:10.1111/dom.14418.

Technology in the management of type 2 diabetes – present status and future prospects

Aldeen Daly, **Roman Hovorka**

[1]Wellcome Trust-MRC Institute of Metabolic Science, University of Cambridge, Cambridge, United Kingdom

rt-CGM IN T2M



Linea Guida della Società Italiana di Diabetologia (SID) e dell'Associazione dei Medici Diabetologi (AMD)

La terapia del diabete mellito di tipo 2

SISTEMA NAZIONALE LINEE GUIDA DELL'ISTITUTO SUPERIORE DI SANITÀ

6.2. MONITORAGGIO GLICEMICO IN CONTINUO

Pazienti con diabete mellito di tipo 2, confronto tra monitoraggio glicemico in continuo (monitoraggio continuo o a scansione) e capillare in pazienti con diabete di tipo 2 trattati con insulina basal-bolus.

Quesito:

Nei pazienti con diabete di tipo 2 in terapia insulinica basal-bolus, è preferibile il monitoraggio in continuo del glucosio sottocute o il monitoraggio tradizionale della glicemia capillare?

Critici: HbA1c (8)
Ipoglicemia severa (8)
Preferenza dei pazienti (7)

Non si suggerisce un monitoraggio glicemico in continuo, al posto del controllo glicemico capillare, per la misurazione della glicemia nei pazienti con diabete mellito di tipo 2 in trattamento insulinico basal-biolus.

Motivazione della raccomandazione

Ci sono pochi studi e di bassa qualità che suggeriscono un piccolo miglioramento dei valori di HbA1c con il monitoraggio continuo della glicemia, senza aumento del rischio ipoglicemico; tuttavia è possibile che il monitoraggio in continuo della glicemia possa in alcuni pazienti peggiorare la qualità della vita. La costo-efficacia del monitoraggio continuo della glicemia dipende dal sistema utilizzato e dal contesto economico e deve essere ulteriormente verificata.

Considerazioni su sottogruppi di pazienti

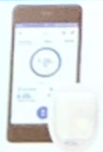
Sebbene non ci siano studi specifici al riguardo, è possibile che soggetti più giovani, con un controllo glicemico non adeguato possano maggiormente beneficiare del monitoraggio in continuo della glicemia; al contrario, soggetti più anziani o con minori abilità tecniche potrebbero avere un impatto negativo sulla propria qualità della vita.

CONTINUOUS SUBCUTANEOUS INSULIN INFUSION (CSII)

Pompa con catetere

Caratteristiche					
Peso (gr)	96	112	110	122	83
Incremento di basale (U)	0.025 (0.025-35)	0.001 (0.001-15)	0.01 (0.05-50)	0.01 (0.02-25)	0.01 (0.00-40
Velocità basali/die (n)	48	16	24	24	24
Profili basali di 24 ore ciascuno (n)	8	6	5	5	2
Frequenza con cui vengono somministrati i boletti di basale (U o min)	????	5 min	3 min	3 min	0.05 u
Target BG (target a cui porta il bolo correttivo)	Range: Corretto al limite massimo o al minimo	Target singolo	Range: Correzione alla metà	Range: correzione alla media	Range: correzione alla metà
Incremento del bolo (U)	0.1 (max 25)	0.01 (max 25)	0.1 (max 25)	0.05 (max 50)	0.1 (max 30)
Allarme di occlusione (h) (1 U/H)	2-3.8 h	2h	<2 h	2.2 h	4 h
Volume di insulina (U)	300	300	300	160	160

Pompa patch (senza catetere)

Caratteristiche				
Peso (gr)	26	29	21,5	34 gr
Incremento di basale (U)	0,05 (0.05-30)	0.01 (0.1-25)	0.05 (0.05-10)	0,05 U/h
Velocità basali/die (n)	24	24	48	48
Profili basali di 24 ore ciascuno (n)	7	5	5	3
Frequenza con cui vengono somministrati i boletti di basale (U o min)	0.05 U	3 min	0.05 U	0,05U
Target BG	Target singolo + soglia	Range : correzione alla metà	Range: correz alla metà	Range:Corretto al limite max o min
Incremento del bolo (U)	0.05 (max 30)	0.05 (max 50)	0.05 (max 25)	0,1 U (max 25)
Allarme di occlusione (h) (1 U/H)	1.5-5.5 h	5 h	< 3 h	4,24 h
Volume di insulina (U)	200	200	200	100 - 200 unità/1-2 mL

CSII vs MDI IN T2D

- Individual patient data meta-analysis and meta-regression of 5 RCTs; 590 pts (287 MDI vs 303 CSII)
- Study duration: 3-24 months
- Baseline HbA1c: 8.1% -9.6%
- Insulin dose: 0.72- 1.16 U/Kg
- Primary outcome: HbA1c at study completion
- Secondary outcomes: insulin dose (TDD and U/Kg), weight at study completion
- Meta-regression covariates: sex, age, study duration, diabetes duration, BL HbA1c level, insulin dose, and weight

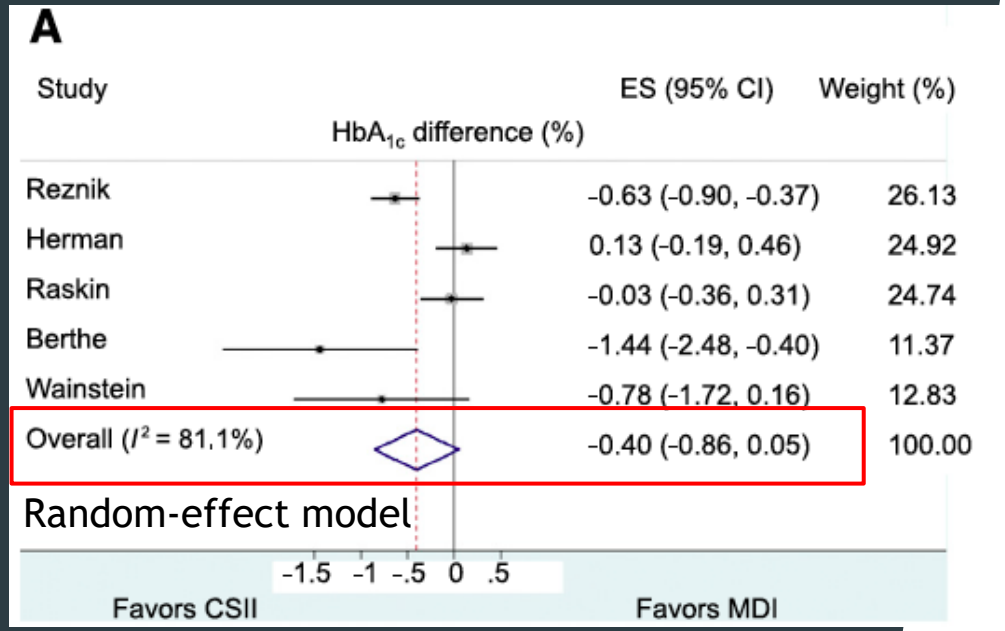
Glycemic Control During Continuous Subcutaneous Insulin Infusion Versus Multiple Daily Insulin Injections in Type 2 Diabetes: Individual Patient Data Meta-analysis and Meta-regression of Randomized Controlled Trials

John C. Pickup,[1] Yves Reznik,[2] and Alex J. Sutton[3]

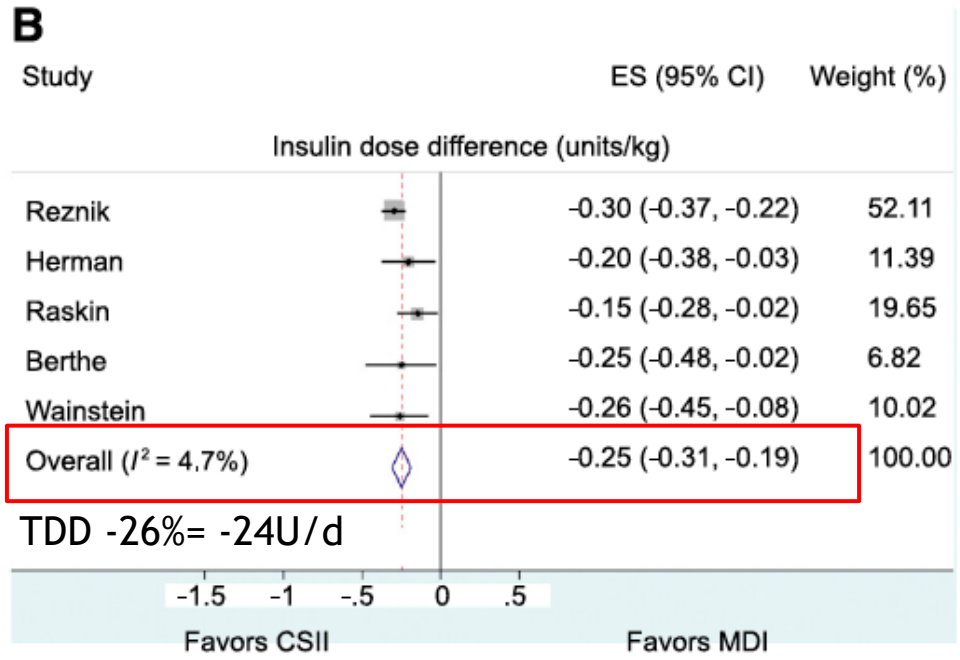
Diabetes Care 2017;40:715–722 | DOI: 10.2337/dc16-2201

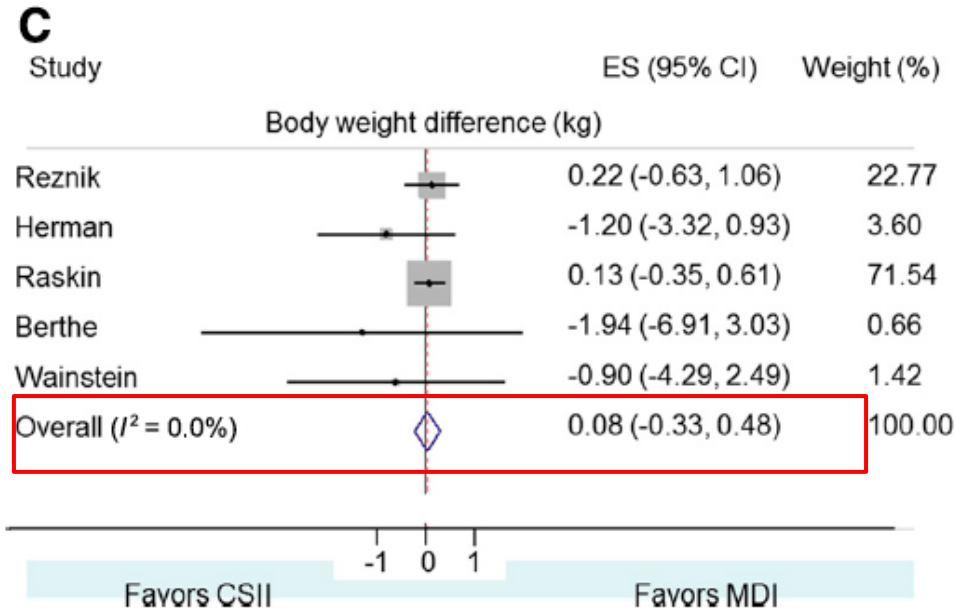
CSII vs MDI IN T2D

INDIVIDUAL PATIENT DATA META-ANALYSIS



Using a fixed-effect model HbA1c difference was lower -0.30% but with a narrower CI (-0.47 to -0.13 favoring CSII





CSII vs MDI IN T2D

- Severe hypoglycaemia → NS
- Nonsevere hypoglycaemia (different definitions) → NS
- Nocturnal hypoglycaemia (1 RCT) → NS
- Quality of life (different questionnaires) → NS

Received: 24 April 2019 | Revised: 4 July 2019 | Accepted: 22 July 2019
DOI: 10.1111/dom.13845

ORIGINAL ARTICLE

WILEY

Impact of technology on glycaemic control in type 2 diabetes: A meta-analysis of randomized trials on continuous glucose monitoring and continuous subcutaneous insulin infusion

Ilaria Dicembrini MD[1,2] | Edoardo Mannucci MD[1,2] | Matteo Monami MD[1] |

TABLE 1 Effects of continuous subcutaneous insulin infusion versus multiple daily injections on quality of life and hypoglycaemia

Study: First author, year	Quality of life	Hypoglycaemia
Berthe et al (2007)[9]	Diabetes treatment satisfaction score[11] CSII vs MDI; MDI better	<60 mg/dL with SMBG or CGM Holter system CSII vs MDI; nonsignificant
Herman et al (2005)[10]	DQoLc+q (ShenwKatsan, 1999) + SF-36 (Wear Sherbourne, 1992) CSII vs MDI; nonsignificant	<65 mg/dL and/or symptoms CSII vs MDI; nonsignificant
Jennings et al (1991)[14]	Treatment satisfaction and general well-being (Bradley and Lewis, 2004) CSII vs MDI; nonsignificant	Self-reported CSII vs MDI; nonsignificant
Raskin et al (2003)[11]	Diabetes treatment satisfaction score[11] CSII vs MDI; better CSII	SMBG <50 mg/dL and/or symptoms CSII vs MDI; nonsignificant
Reznik et al (2014)[12]	Treatment satisfaction and general well-being (Bradley and Lewis 1990) CSII vs MDI; not reported	CGM Holter system or SMBG <70 mg/dL CSII vs MDI; nonsignificant
Wainstein et al (2004)[13]	Not measured	SMBG <60 mg/dL CSII vs MDI; nonsignificant

Abbreviations: CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; SMBG, self-monitoring of blood glucose.

Linea Guida della Società Italiana di Diabetologia (SID) e dell'Associazione dei Medici Diabetologi (AMD)

La terapia del diabete mellito di tipo 2

SISTEMA NAZIONALE LINEE GUIDA DELL'ISTITUTO SUPERIORE DI SANITÀ

5.6. TERAPIA INSULINICA CON MICROINFUSORI

Pazienti con diabete mellito di tipo 2 non adeguatamente controllato in trattamento con iniezioni multiple di insulina, confronto tra somministrazione di insulina mediante microinfusori e iniezioni multiple.

Quesito

Nei pazienti con diabete di tipo 2 non adeguatamente controllati dalla terapia con insulina basal-bolus, è utile l'uso del microinfusore?

Critici: Ipoglicemia severa (8)
HbA1c (8)
Qualità della vita (7)
Preferenze del paziente (7)

L'utilizzo routinario del microinfusore di insulina nei pazienti con diabete di tipo 2 non adeguatamente controllati non è raccomandato.

Motivazione della raccomandazione

Non ci sono evidenze di reali vantaggi derivanti dall'uso del microinfusore nei pazienti con diabete di tipo 2 rispetto alla terapia multi-iniettiva. Inoltre i costi per tale terapia sono molto elevati.
La qualità delle evidenze è molto bassa per la maggior parte degli *outcome* critici, in particolare per il disegno in aperto della maggior parte degli studi inclusi, la presenza di elevata eterogeneità e la scarsa numerosità di pazienti arruolati.
Non ci sono studi specifici di natura economica per valutare la costo-efficacia dell'intervento proposto in pazienti con diabete di tipo 2.

Considerazioni su sottogruppi di pazienti

I microinfusori potrebbero avere dei vantaggi in alcuni specifici sottogruppi di pazienti con diabete di tipo 2 come quelli con necessità di basalizzazione diversa durante le ore notturne, ovvero i pazienti che non riescono a controllare la glicemia al risveglio perché le esistenti formulazioni di insuline basali non permettono la necessaria flessibilità. Mancano tuttavia studi o analisi per sottogruppo che prendano in considerazioni questa categoria di pazienti con diabete di tipo 2.

TECNOLOGIA APPLICATA AL T2D: THM

- EVIDENZE DERIVATE DA POCHI STUDI, ETROGENEI E DI BASSA QUALITA'
- INIZIALI SEGNALI POSITIVI: ↓ ipoglicemia (FGM), ↓ HbA1c (rt-CGM/CSII), ↓ TDD (CSII), QoL ???
- NECESSITA' DI SELEZIONARE GLI USERS: GIOVANI, MOTIVATI, DISCRETA ALFABETIZZAZIONE DIGITALE, COMPENSO PEGGIORE
- DEVICES SEMPLICI SENZA TECNOLOGIA COMPLESSA
- NO STUDI CON SISTEMI INTEGRATI

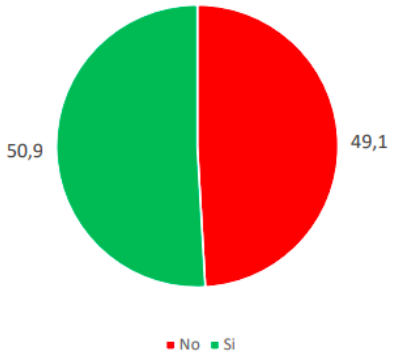
Table 4. Preferable Characteristics of an Insulin Pump Intended for Patients With T2DM.

Characteristics of an insulin pump intended for T2DM	
Intended for	T2DM
Kind of pump	Patch pump
Basal rate	One to two basal rate profiles with three segments (every 8 h)
Bolus types	One standard bolus with predefined dose
Insulin reservoir	3 mL/300 U prefilled
Insulin	U-500, U-300, U-200, U-100
Additional features	CGM connectivity/share the care opportunity

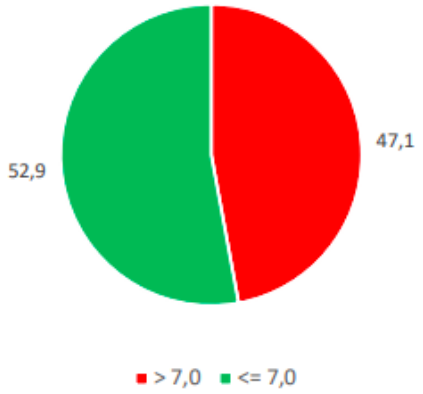
Freckmann G. et al., J Diab Sci Technol 2021

Soggetti con HbA1c ≤ 7.0%

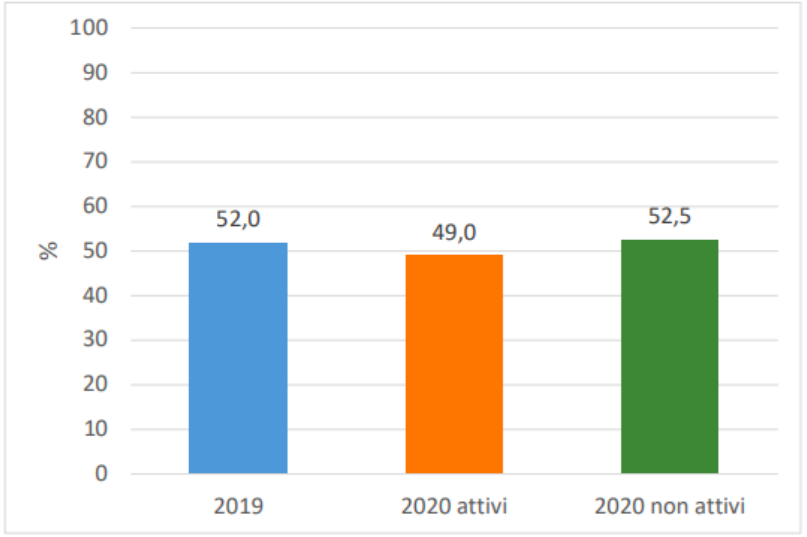
DM2



Soggetti con HbA1c ≤ 7,0% (%)

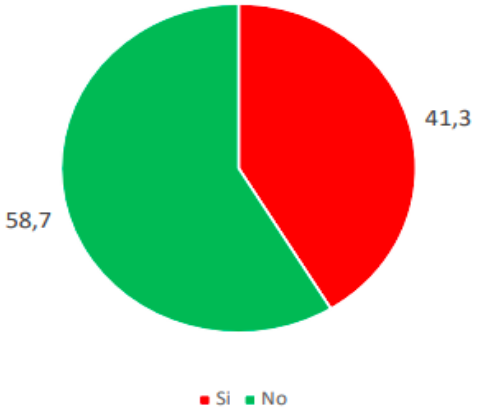


Soggetti con HbA1c ≤ 7,0%

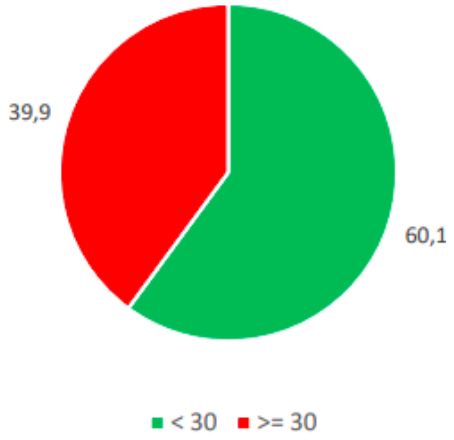


Soggetti con BMI ≥30 Kg

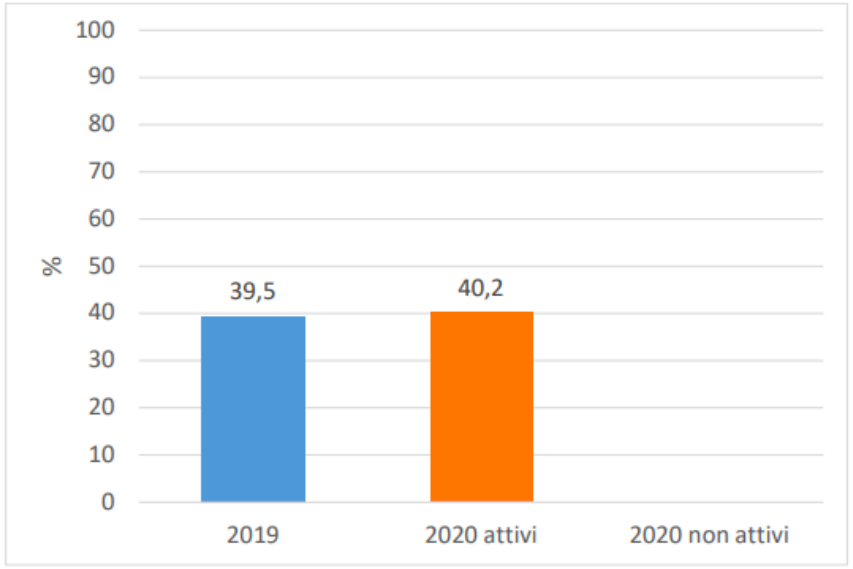
DM2



etti con BMI ≥30 Kg/m²

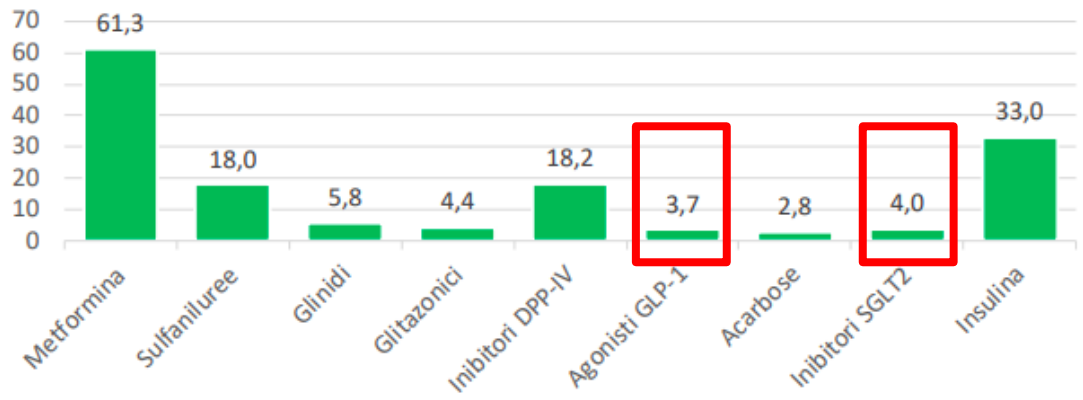


Soggetti con BMI ≥30 Kg/m²

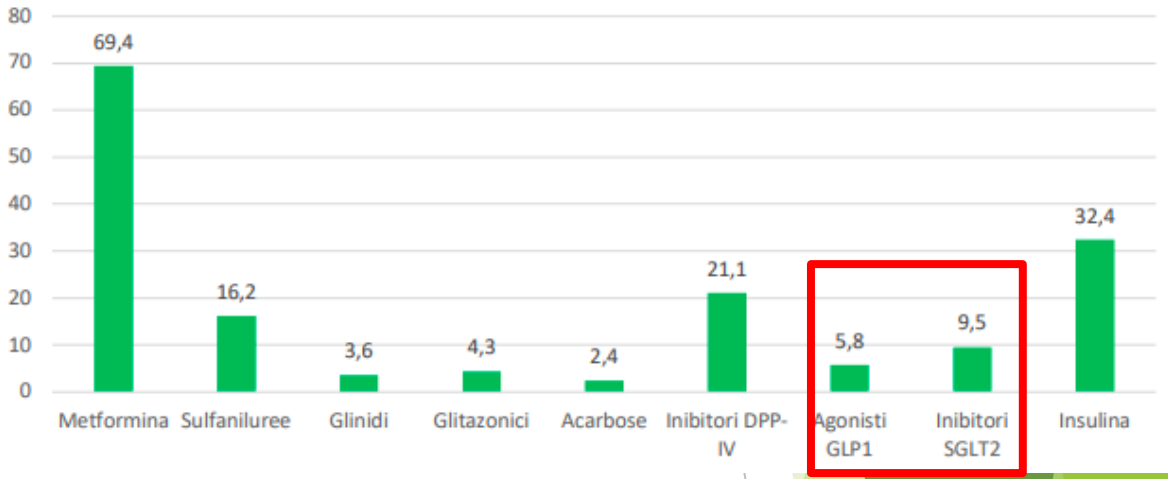


Soggetti con HbA1c ≤ 7.0%

Distribuzione dei pazienti con DM2 per classe di farmaco ipoglicemizzante (%)



Distribuzione dei pazienti con DM2 per classe di farmaco ipoglicemizzante (%)



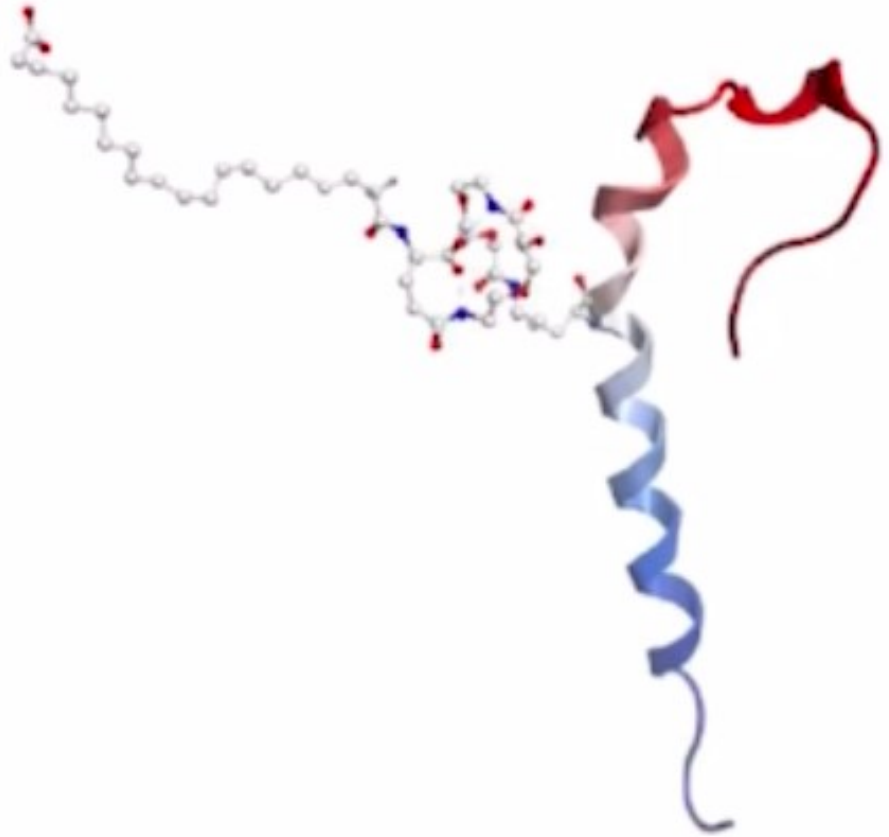
Distribuzione dei pazienti con DM2 per classe di farmaco anti-iperglicemizzante (%)

Annali AMD 2021

Trattamento	2019	2020 ATTIVI	2020 NON ATTIVI
Metformina	71,0	71,8	63,3
Sulfanilurea	14,0	12,9	13,0
Glinide	2,7	2,2	3,3
Glitazone	4,5	4,5	4,0
Acarbose	2,0	1,8	1,9
DPPIVi	21,9	22,5	26,0
GLP1-RA	10,9	15,7	9,8
SGLT2i	12,1	16,6	11,7
Insulina	32,8	34,6	37,2
Insulina basale	28,1	29,5	31,7
Insulina rapida	19,2	19,4	23,1

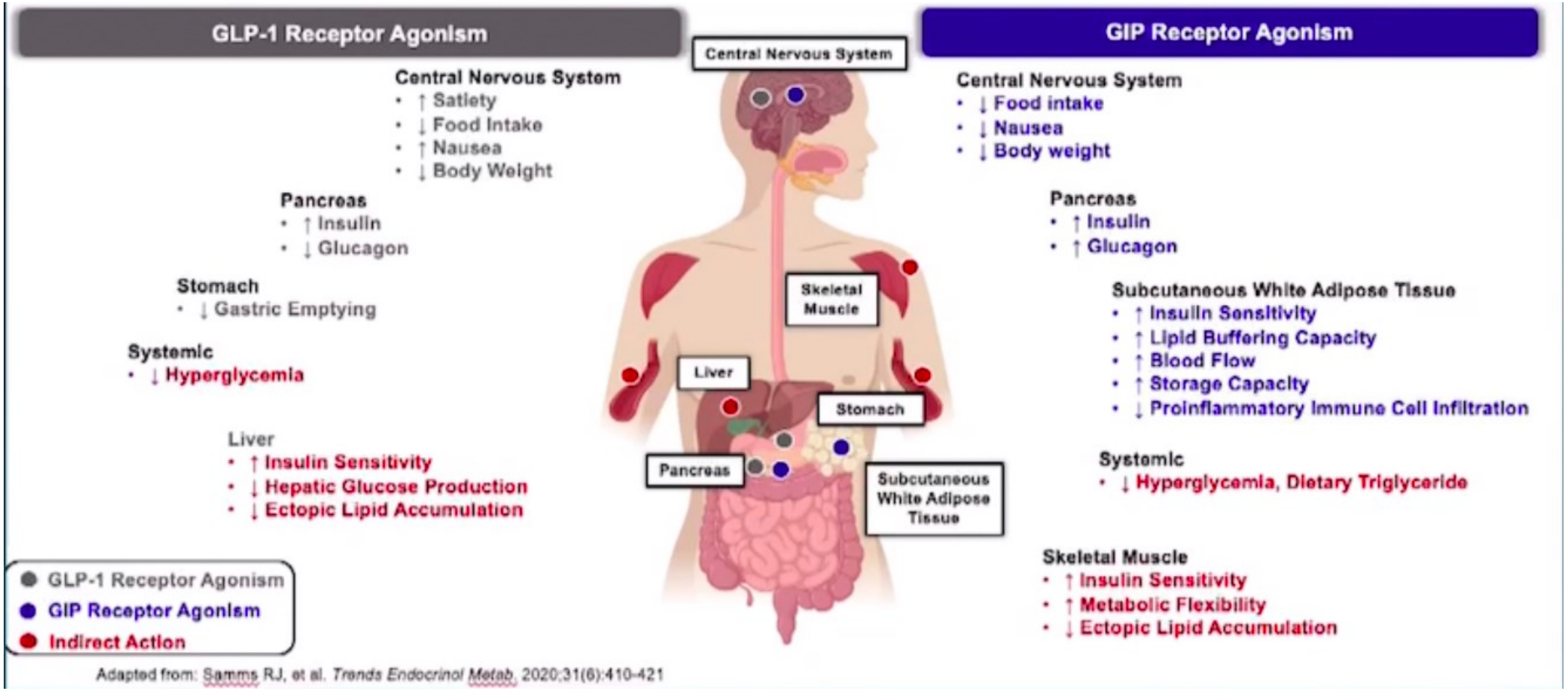
Tirzepatide: a Dual GIP/GLP-1 Receptor Agonist

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

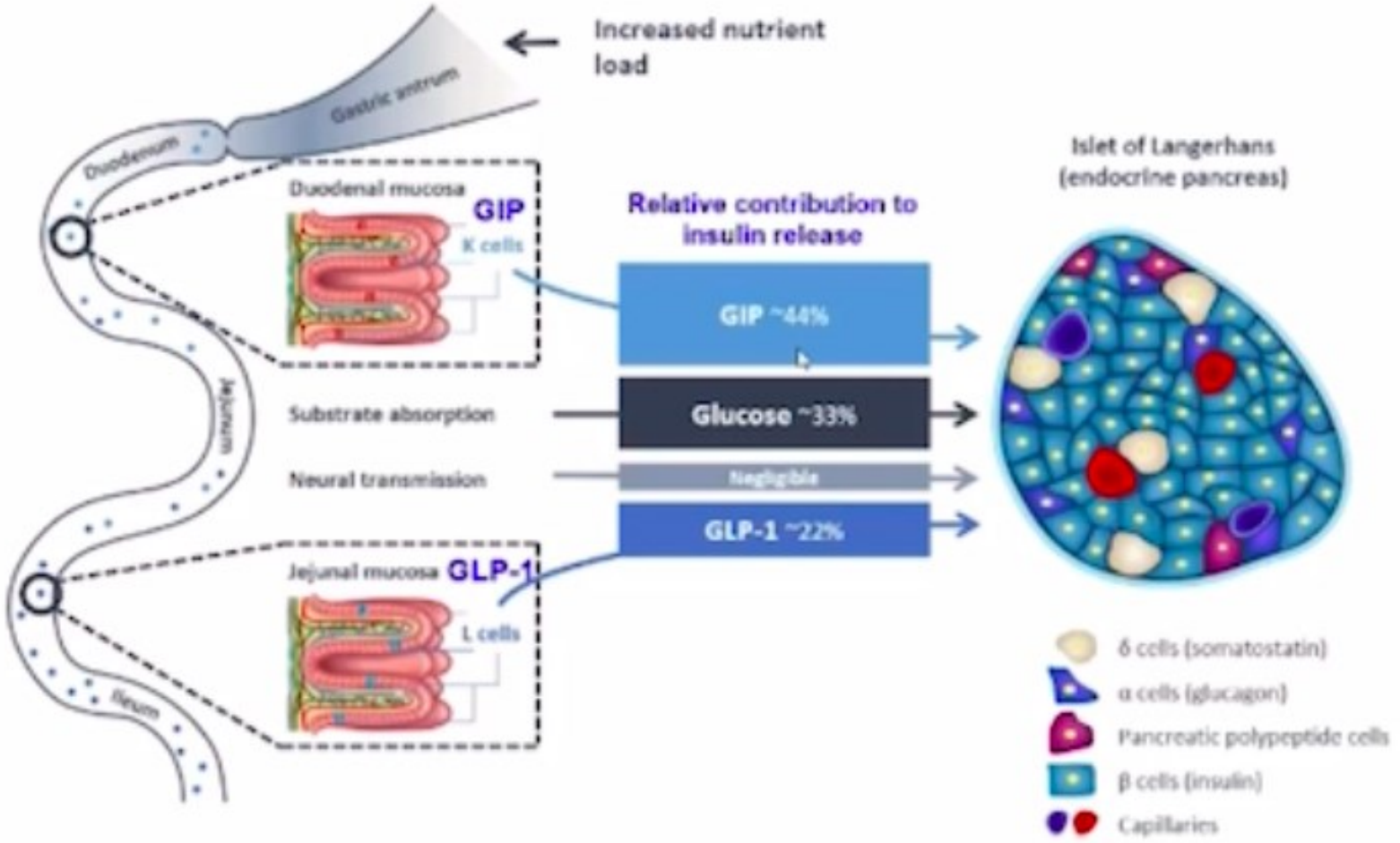


GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1

Coskun T, et al. *Mol Metab* 2018;18:3-14

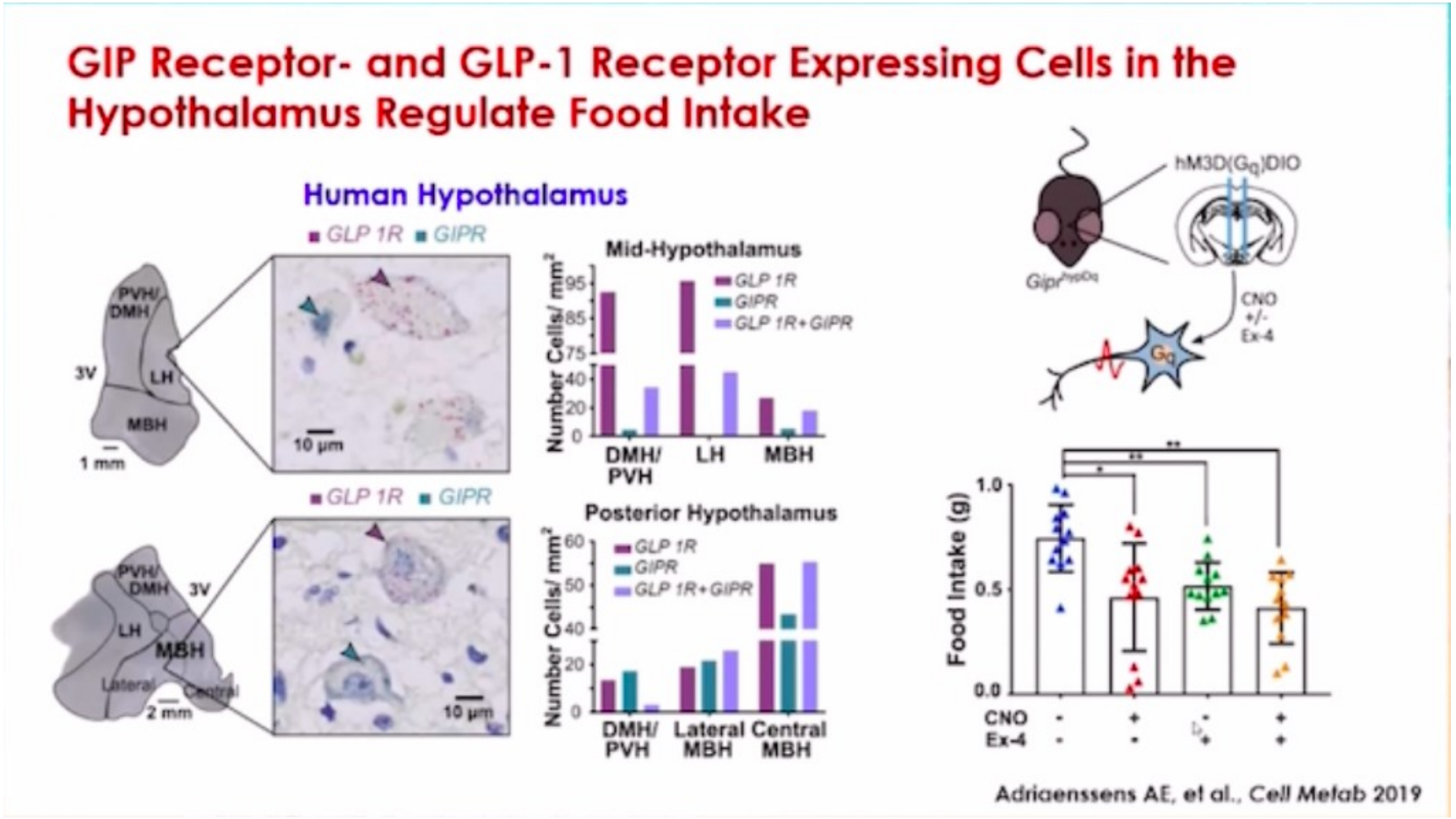

GLP-1 Receptor Agonism
Central Nervous System
• ↑ Satiety
• ↓ Food Intake
• ↑ Nausea
• ↓ Body Weight
Pancreas
• ↑ Insulin
• ↓ Glucagon
Stomach
• ↓ Gastric Emptying
Systemic
• ↓ Hyperglycemia
Liver
• ↑ Insulin Sensitivity
• ↓ Hepatic Glucose Production
• ↓ Ectopic Lipid Accumulation
GLP-1 Receptor Agonism
GIP Receptor Agonism
Indirect Action
Central Nervous System
Skeletal Muscle
Liver
Stomach
Pancreas
Subcutaneous White Adipose Tissue
GIP Receptor Agonism
Central Nervous System
• ↓ Food intake
• ↓ Nausea
• ↓ Body weight
Pancreas
• ↑ Insulin
• ↑ Glucagon
Subcutaneous White Adipose Tissue
• ↑ Insulin Sensitivity
• ↑ Lipid Buffering Capacity
• ↑ Blood Flow
• ↑ Storage Capacity
• ↓ Proinflammatory Immune Cell Infiltration
Systemic
• ↓ Hyperglycemia, Dietary Triglyceride
Skeletal Muscle
• ↑ Insulin Sensitivity
• ↑ Metabolic Flexibility
• ↓ Ectopic Lipid Accumulation
Adapted from: Samms RJ, et al. Trends Endocrinol Metab. 2020;31(6):410-421

The Incretin Hormones GIP and GLP-1 Signal to the Pancreas

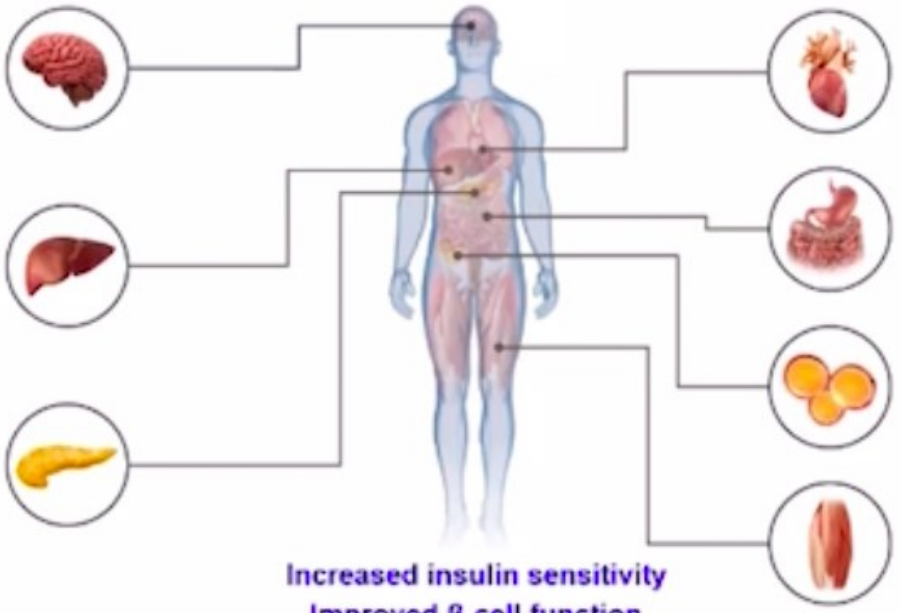


- Nutrient load in the gut stimulates release of the incretin hormones GIP and GLP-1
- GIP and GLP-1 signal to pancreatic islets to enhance glucose-dependent insulin secretion and subsequent PPG clearance in healthy people

GIP Receptor- and GLP-1 Receptor Expressing Cells in the Hypothalamus Regulate Food Intake



Potential MOAs of Tirzepatide Under Investigation



CNS
Appetite, feeding behaviour, energy expenditure, and nausea

Liver
Insulin sensitivity, lipid metabolism, and energy expenditure

Pancreas: islets
Secretion of insulin and glucagon

Cardiovascular
Plasma lipids, inflammation, and endothelial function

GI tract: stomach
Delayed gastric emptying

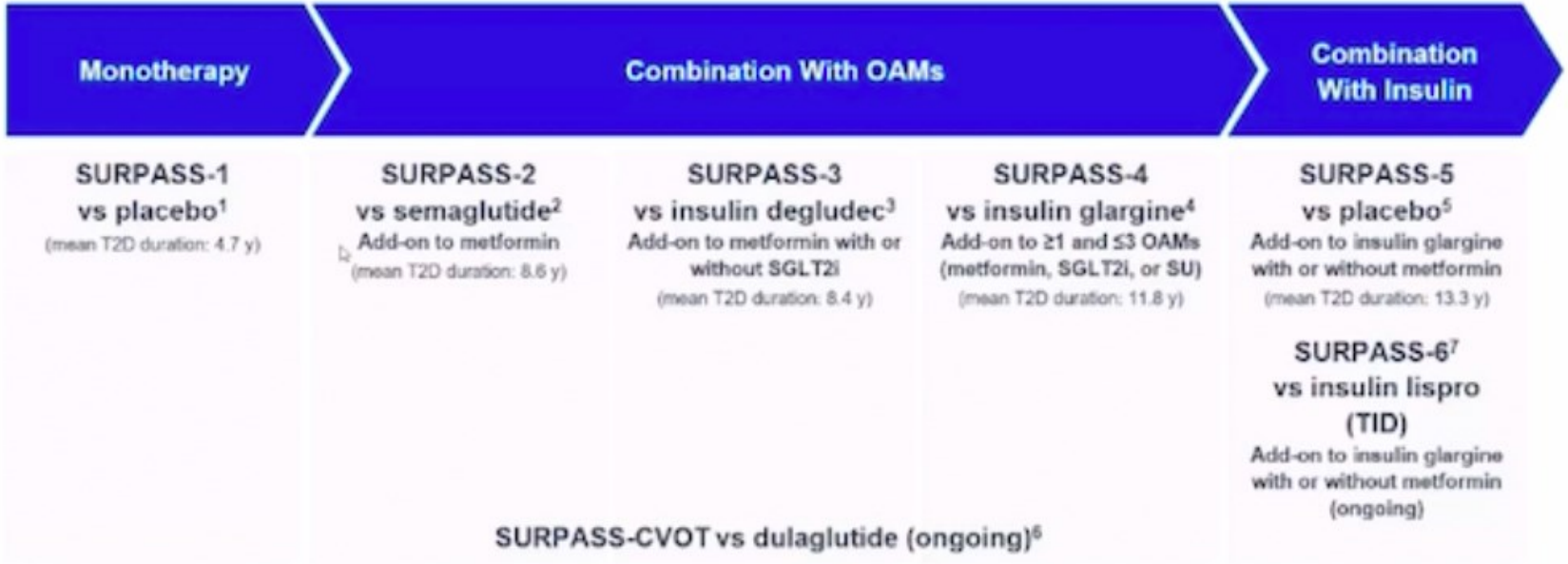
Adipose tissue
Lipid metabolism and insulin sensitivity

Skeletal muscle
Insulin sensitivity and glucose disposal

Increased insulin sensitivity
Improved β-cell function
Reduced food intake
Increased energy expenditure
Improved metabolic flexibility and nutrient partitioning
Different adverse event profile vs GLP-1 RA

CNS = central nervous system; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; MOA = mechanism of action; RA = receptor agonist.

SURPASS Clinical Trial Programme



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 Program: Change in HbA1c from Baseline

Trial	N	Primary endpoint (weeks)	Baseline HbA_{1c} (%)	Comparator	Change from baseline in HbA_{1c} (%) at primary endpoint			
					Comparator	TZP 5 mg	TZP 10 mg	TZP 15 mg
SURPASS-1 (naïve)	478	40	7.95	Placebo OW	0.04	-1.87*	-1.89*	-2.07*
SURPASS-2 (metformin)	1878	40	8.28	Semaglutide 1 mg OW	-1.86	-2.09*	-2.37*	-2.46*
SURPASS-3 (metformin ± SGLT-2i)	1437	52	8.18	Insulin degludec OD	-1.34	-1.93*	-2.20*	-2.37*
SURPASS-4 (metformin ± SU ± SGLT-2i)§	2002	52	8.52	Insulin glargine OD	-1.44	-2.24*	-2.43*	-2.58*
SURPASS-5 (insulin glargine ± metformin)	475	40	8.31	Placebo OW	-0.93	-2.23*	-2.59*	-2.59*

TZP, tirzepatide; OW, once-weekly; OD, once-daily; SU, sulfonylurea; SGLT-2i, SGLT-2 inhibitors; *statistical significance vs. comparator

SURPASS Program: Proportion of Patients Achieving HbA1c <7%

Trial	N	Primary endpoint (weeks)	Baseline HbA_{1c} (%)	Comparator	Proportion of patients (%) achieving HbA_{1c}<7% at primary endpoint			
					Comparator	TZP 5 mg	TZP 10 mg	TZP 15 mg
SURPASS-1 (naïve)	478	40	7.95	Placebo OW	19.6	86.8*	91.5*	87.9*
SURPASS-2 (metformin)	1878	40	8.28	Semaglutide 1 mg OW	81.1	85.5*	88.9*	92.2*
SURPASS-3 (metformin ± SGLT-2i)	1437	52	8.18	Insulin degludec OD	61.3	82.4*	89.7*	92.6*
SURPASS-4 (metformin ± SU ± SGLT-2i)§	2002	52	8.52	Insulin glargine OD	50.7	81.0*	88.2*	90.7*
SURPASS-5 (insulin glargine ± metformin)	475	40	8.31	Placebo OW	33.9	93.0*	97.4*	94.0*

TZP, tirzepatide; OW, once-weekly; OD, once-daily; SU, sulfonylurea; SGLT-2i, SGLT-2 inhibitors; *statistical significance vs. comparator

SURPASS Program: Proportion of Patients Achieving HbA1c <5.7%

Trial	N	Primary endpoint (weeks)	Baseline HbA_{1c} (%)	Comparator	Proportion of patients (%) achieving HbA_{1c}<5.7% at primary endpoint			
					Comparator	TZP 5 mg	TZP 10 mg	TZP 15 mg
SURPASS-1 (naïve)	478	40	7.95	Placebo OW	0.9	33.9*	30.5*	51.7*
SURPASS-2 (metformin)	1878	40	8.28	Semaglutide 1 mg OW	19.7	29.3*	44.7*	50.9*
SURPASS-3 (metformin ± SGLT-2i)	1437	52	8.18	Insulin degludec OD	5.4	25.8*	38.6*	48.4*
SURPASS-4 (metformin ± SU ± SGLT-2i)§	2002	52	8.52	Insulin glargine OD	3.4	23.0#	32.7#	43.1#
SURPASS-5 (insulin glargine ± metformin)	475	40	8.31	Placebo OW	2.5	26.1*	47.8*	62.4*

TZP, tirzepatide; OW, once-weekly; OD, once-daily; SU, sulfonylurea; SGLT-2i, SGLT-2 inhibitors; *statistical significance vs. comparator

SURPASS Program: Change in Body Weight from Baseline

Trial	N	Primary endpoint (weeks)	Baseline weight (kg)	Comparator	Change from baseline in body weight (kg) at primary endpoint			
					Comparator	TZP 5 mg	TZP 10 mg	TZP 15 mg
SURPASS-1 (naïve)	478	40	85.8	Placebo OW	-0.7	-7.0*	-7.8*	-9.5*
SURPASS-2 (metformin)	1878	40	93.8	Semaglutide 1 mg OW	-6.2	-7.8*	-10.3*	-12.4*
SURPASS-3 (metformin ± SGLT-2i)	1437	52	94.5	Insulin degludec OD	+2.3	-7.5*	-10.7*	-12.9*
SURPASS-4 (metformin ± SU ± SGLT-2i)§	2002	52	90.3	Insulin glargine OD	+1.9	-7.1*	-9.5*	-11.7*
SURPASS-5 (insulin glargine ± metformin)	475	40	95.3	Placebo OW	+1.7	-6.2*	-8.2*	-10.9*

TZP, tirzepatide; OW, once weekly; OD, once daily; SU, sulfonylurea; SGLT-2i, SGLT-2 inhibitors; *statistical significance vs. comparator

SURPASS Program: Tirzepatide in Context

- Largest extent of HbA1c reduction (**-1.87%** to **-2.59%**)
- Highest proportion of patients at HbA1c target <7% (**81%** to **97.4%**)
- Highest proportion of patient with normal HbA1c (**23.0%** to **62.4%**)
- Largest extent of body weight reduction (**-6.2 kg** to **-12.9 kg**)
- Efficacy with different background therapies (**naïve**, **metformin only**, **2-3 OAD**, **basal insulin**) and diabetes durations (**4.7 yrs**, **8.4 yrs**, **8.6 yrs**, **11.8 yrs**, **13.3 yrs**)
- No excess risk of hypoglycemia
- GI tolerability similar to GLP-1RA class

Highest level of glucose control

Use in early as well as late T2D

Combination with OAD as well as with insulin

Highest degree of weight loss

Potential for T2D regression


Grazie