



CLINICAL DEBATE - REMISSIONE DEL DIABETE TIPO 2

Terapia farmacologica

DANILA FAVA

UOSD Endocrinologia e Diabetologia

AO S.Giovanni Addolorata _ Roma

La dott.ssa Danila Fava ai sensi dell' art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell' Accordo Stato – Regione del 5 novembre 2009 dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Novo Nordisk
- Movì
- Daiichi Sankyo

Remissione nel diabete tipo 2: definizione

Diabetologia (2021) 64:2359–2366
<https://doi.org/10.1007/s00125-021-05542-z>

CONSENSUS REPORT



Consensus report: definition and interpretation of remission in type 2 diabetes

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« a return of HbA1c to <6.5% (or FPG <126 mg/dL or CGM-derived eA1C <6.5%) that occurs spontaneously or following an intervention and that persists for at least 3 months in the absence of usual glucose-lowering pharmacotherapy »

Remissione nel diabete tipo 2: quali interventi per ottenerla?

Table 1—Interventions and temporal factors in determining remission of T2D		
Intervention <i>Note: Documentation of remission should include a measurement of HbA_{1c} just prior to intervention</i>	Interval before testing of HbA _{1c} can reliably evaluate the response	Subsequent measurements of HbA _{1c} to document continuation of a remission
Pharmacotherapy	At least 3 months <u>after cessation of this intervention</u>	Not more often than every 3 months nor less frequent than yearly
Surgery	At least 3 months after the procedure <i>and</i> 3 months <u>after cessation of any pharmacotherapy</u>	
Lifestyle	At least 6 months after beginning this intervention <i>and</i> 3 months <u>after cessation of any pharmacotherapy</u>	

Interruzione dell'intervento

La chirurgia bariatrica è un trattamento permanente

Lo stile di vita salutare viene mantenuto

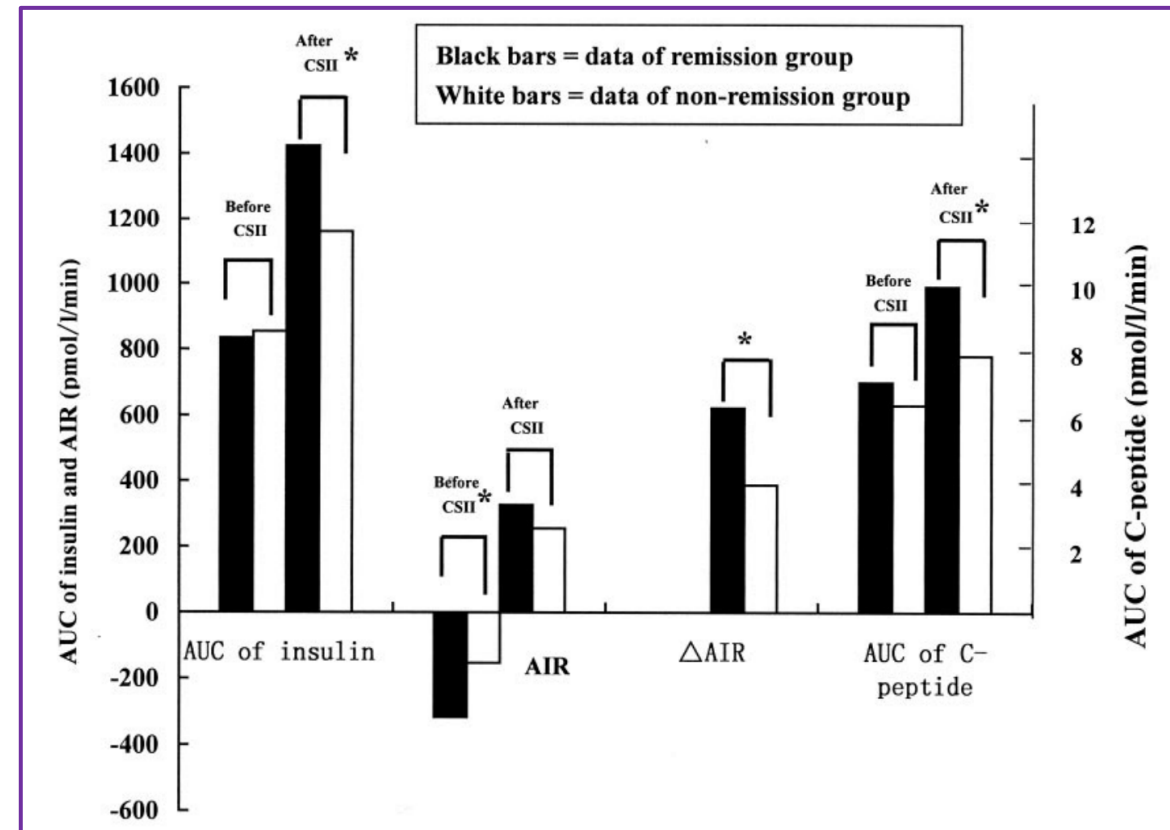
La terapia insulinica intensiva a breve termine nel DM2 di nuova diagnosi è associata al miglioramento della funzione β cellulare a lungo termine

Table 2—Clinical characteristics in the remission and nonremission groups

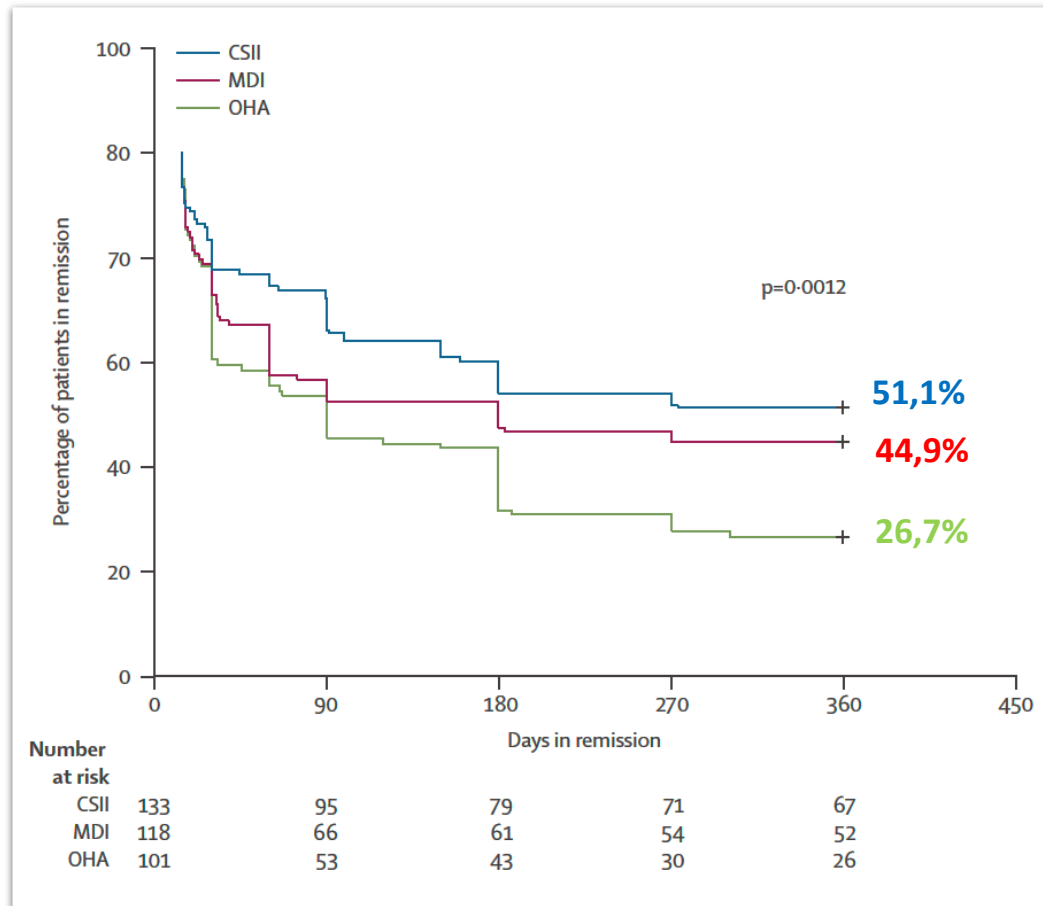
Item	Remission	Nonremission	P
n	32	36	—
Age (years)	50.6 $\pm$ 10.4	51.6 $\pm$ 13.1	0.718
BMI before CSII (kg/m ²)	25.9 $\pm$ 4.3	24.3 $\pm$ 3.1	0.069
BMI after CSII (kg/m ²)	26.0 $\pm$ 4.2	24.3 $\pm$ 3.0	0.051
HbA _{1c} before CSII (%)	10.3 $\pm$ 1.9	10.0 $\pm$ 1.9	0.647
HbA _{1c} after CSII (%)	9.2 $\pm$ 2.0	8.6 $\pm$ 1.5	0.207
FPG before CSII (mmol/l)	14.9 $\pm$ 3.0	14.7 $\pm$ 5.0	0.852
FPG after CSII (mmol/l)	6.1 $\pm$ 1.2	6.7 $\pm$ 1.1*	0.035
PPBG before CSII (mmol/l)	21.7 $\pm$ 5.1	19.7 $\pm$ 5.5	0.141
PPBG after CSII (mmol/l)	8.8 $\pm$ 2.2	9.9 $\pm$ 2.4	0.064

Soggetti in remissione:

- 73% a 3 mesi
- 67% a 6 mesi
- 47% a 12 mesi
- 42% a 24 mesi



La terapia insulinica intensiva nel DM2 di nuova diagnosi aumenta la possibilità di remissione rispetto alla terapia convenzionale



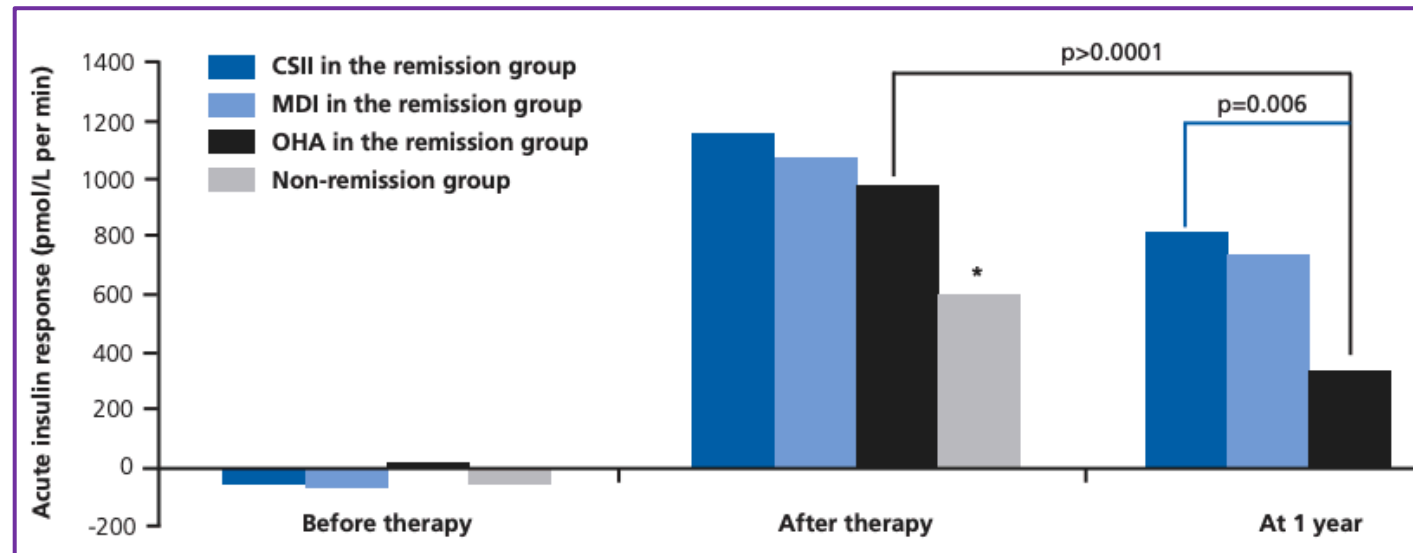
Effect of intensive insulin therapy on β -cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial

Glycaemic goals:	FPG: <110 mg/dl 2-hr after each meal: <144 mg/dl
Treatment:	maintained for 2 weeks after reaching glycaemic targets
Remission:	optimum glycaemic control $\geq$ 12 months without medication
Non-remission:	FPG > 126 mg/dl or 2-hr pp glucose > 180 mg/dl

La terapia insulinica intensiva nel DM2 di nuova diagnosi migliora la funzione delle β cellule

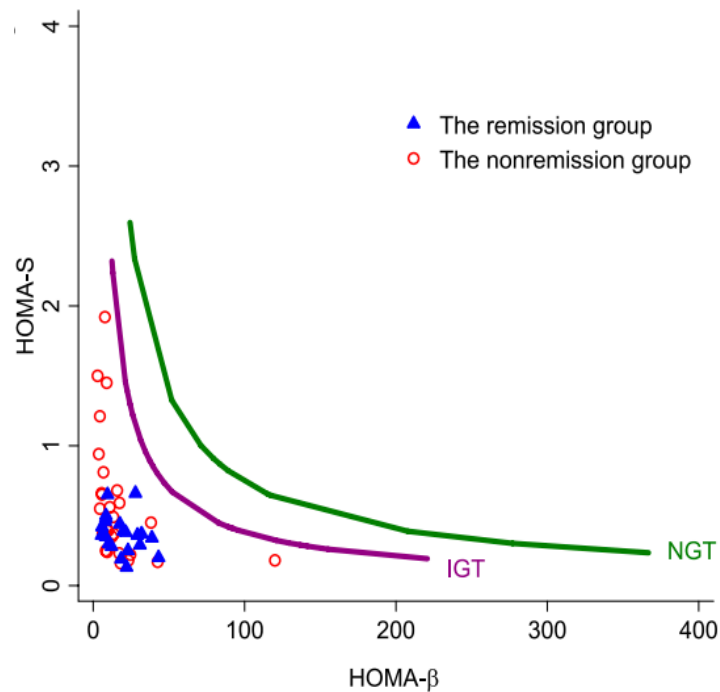
	CSII	MDI	Oral hypoglycaemic agents
Acute insulin response (pmol/L per min) [†]			
Before therapy	-62 (421) (n=126)	-7 (347) (n=114)	-95 (452) (n=95)
After therapy*	889 (1087) (n=129)	793 (1150) (n=115)	736 (1289) (n=90)
PI/IRI (%) [†]			
Before therapy	23.8 (17.5) (n=123)	26.5 (22.6) (n=115)	28.4 (22.2) (n=95)
After therapy*	12.1 (11.8) (n=113)	16.8 (20.1) (n=105)	21.2 (20.7) [‡] (n=90)
HOMA B [†]			
Before therapy	33.6 (45.6) (n=114)	38.3 (36.9) (n=108)	50.0 (60.6) (n=94)
After therapy*	87.5 (82.5) (n=113)	78.9 (65.2) (n=103)	102.3 (16.0) (n=90)
HOMA IR [†]			
Before therapy	6.0 (5.6) (n=114)	6.7 (5.7) (n=108)	6.9 (8.6) (n=94)
After therapy*	3.2 (2.8) (n=113)	3.1 (2.9) (n=103)	4.8 (4.8) (n=90)

Data are mean (SD) unless otherwise indicated. *p<0.0001 compared with before treatment. [†]Data are median (IQR). [‡]p<0.05 compared with CSII.

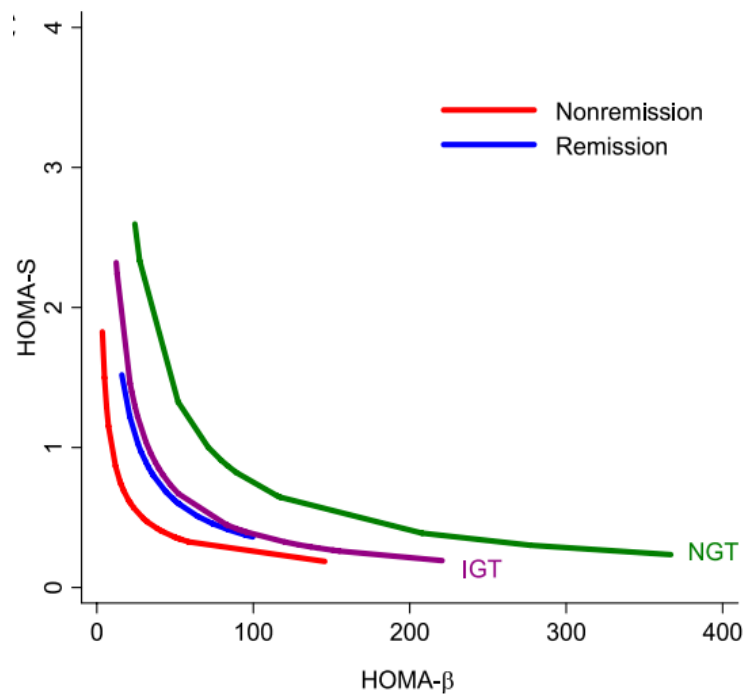


La terapia insulinica intensiva nel DM2 di nuova diagnosi ripristina parzialmente la sensibilità all'insulina e la funzione delle cellule B nei soggetti con remissione

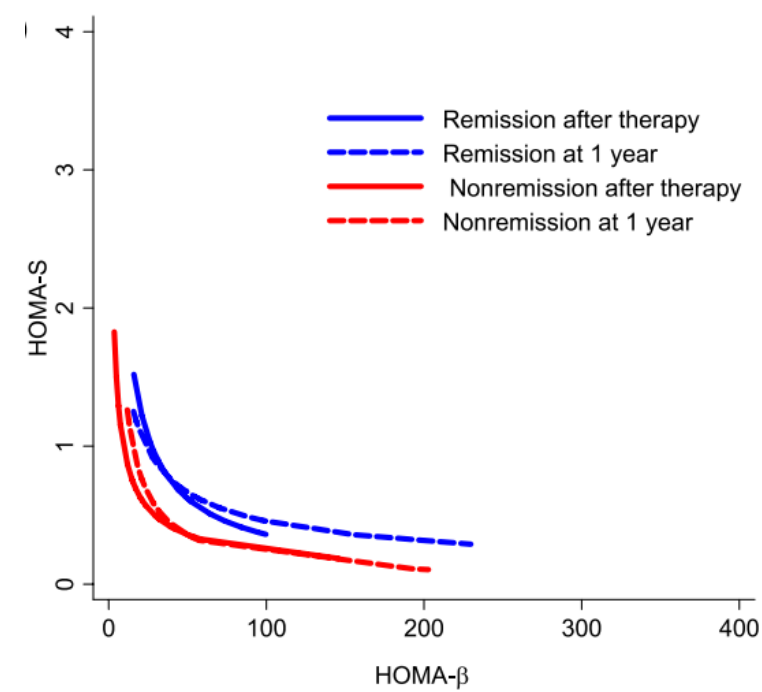
Before therapy



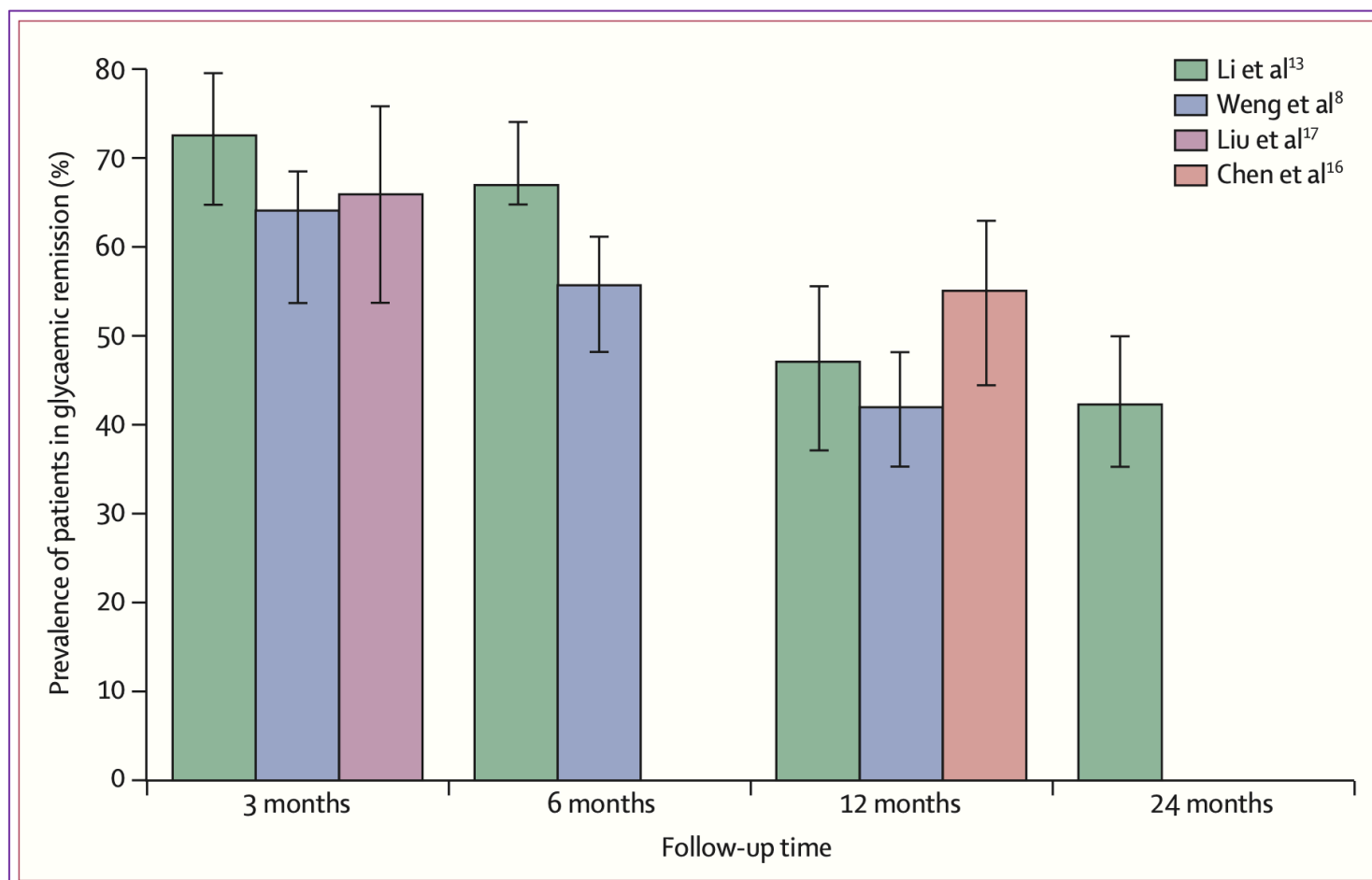
After 2 weeks



After 1 year



Terapia insulinica intensiva nel DM2 di nuova diagnosi e percentuale di remissione a 12 o 24 mesi di follow-up



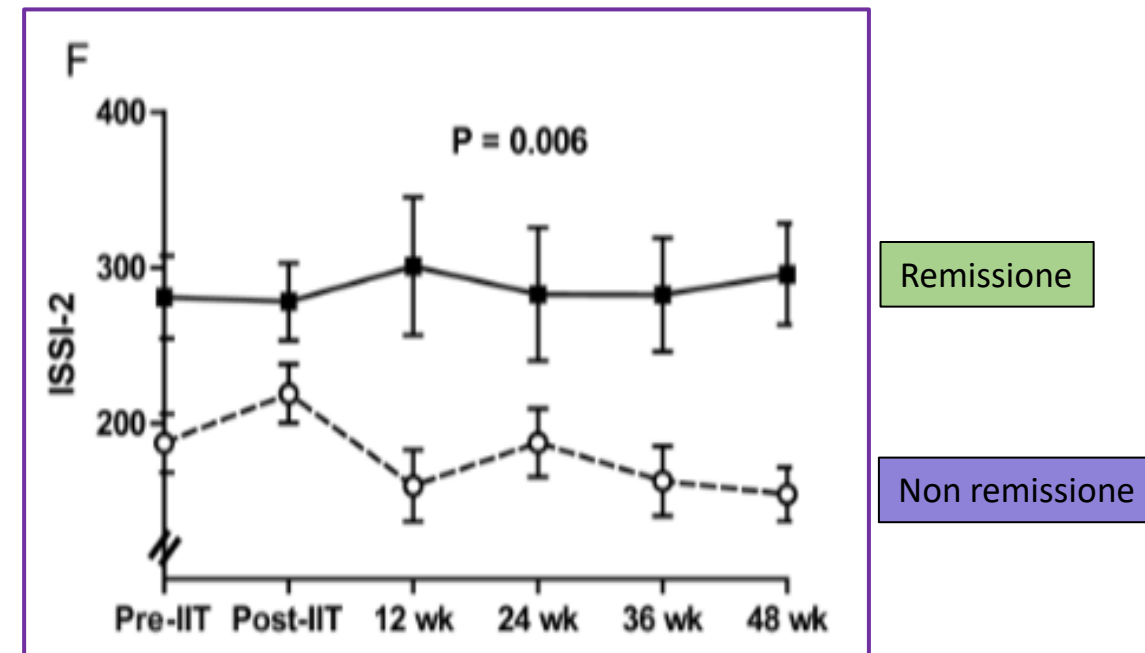
Nell' "early" DM2 la probabilità di remissione dopo terapia insulinica intensiva correla con la durata di malattia ed il valore di HbA1c

BMJ Open
Diabetes
Research
& Care

Predictors of sustained drug-free diabetes remission over 48 weeks following short-term intensive insulin therapy in early type 2 diabetes

56% dei paziente in remissione (A1c<6.5%) a 48 settimane

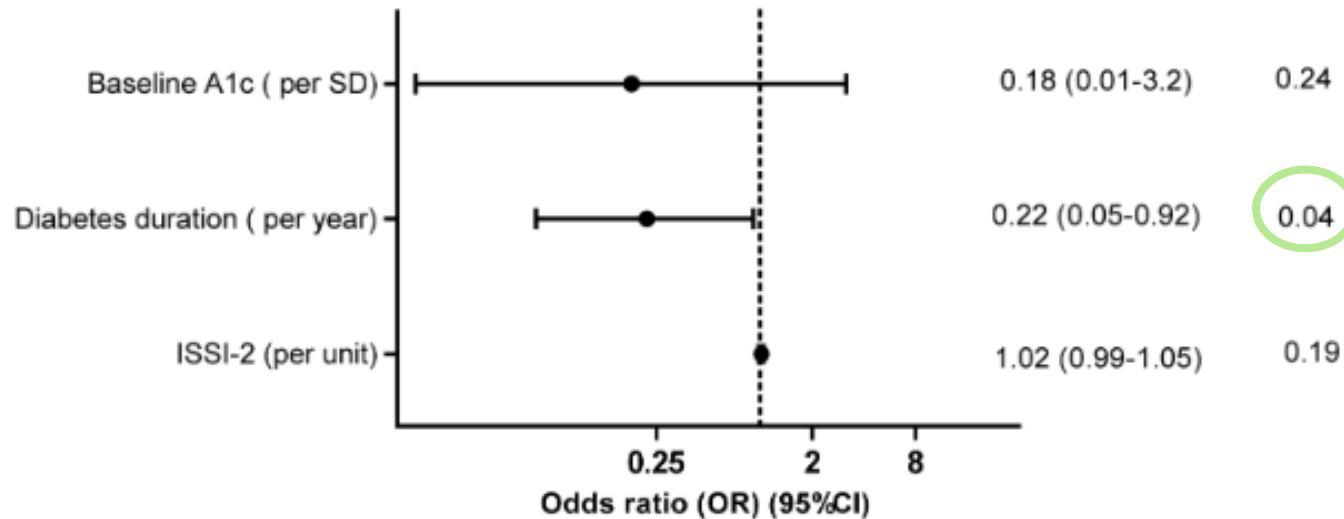
CARATTERISTICHE DELLA POPOLAZIONE AL TEMPO 0		
	NON REMISSIONE	REMISSIONE
Duration of diabetes (years)	2.6±1.8	1.2±1.0
Body mass index (kg/m2)	30.0±4.7	31.5±6.8
Waist circumference (cm)	103.5±12.3	105.0±15.0
Fasting plasma glucose (mmol/L)	6.5±1.3	5.9±0.8
A1c (%)	7.1±0.9	6.2±0.5. *
Matsuda index	4.9 (2.8–7.1)	5.8 (3.5–9.0)
HOMA-IR	5.0 (2.9–7.2)	3.4 (2.3–6.1)
ISSI-2	206 (145–233)	251 (210–341) *



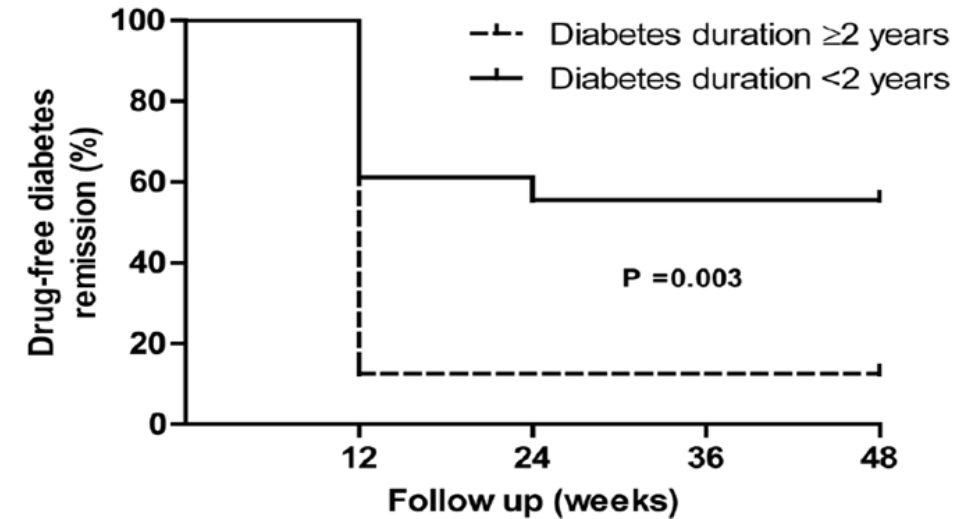
Andamento di ISSI-2 nei 2 gruppi

L'intervento precoce dopo la diagnosi è il principale predittore della remissione del diabete

REMISSIONE DEL DIABETE A 48 MESI



TEMPO DI PERDITA DELLA REMISSIONE DEL DIABETE



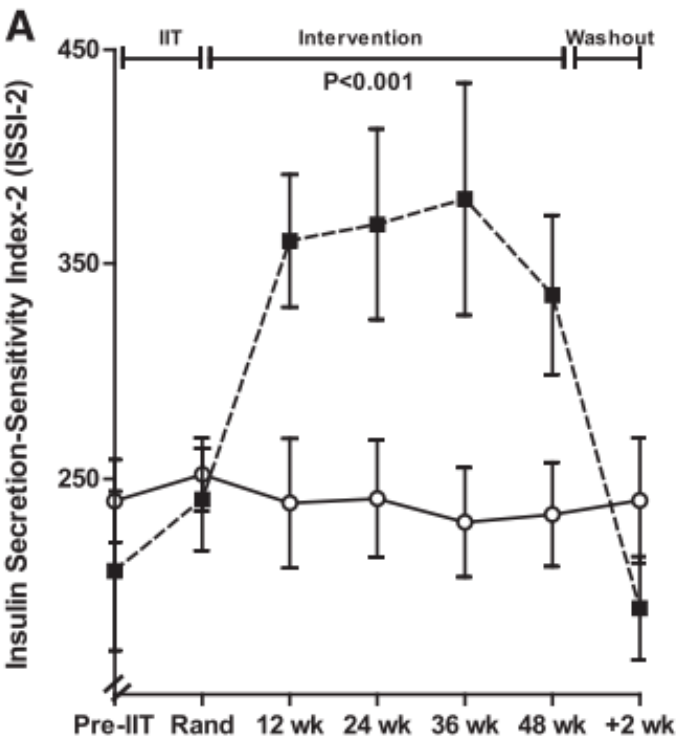
Nell’ “early” DM2 il pre-trattamento insulinico intensivo non assicura il mantenimento a lungo termine degli effetti di liraglutide sulla funzione β cellulare

Liraglutide and the Preservation of Pancreatic β -Cell Function in Early Type 2 Diabetes: The LIBRA Trial

Diabetes Care 2014;37:3270–3278 | DOI: 10.2337/dc14-0893

Table 1—Baseline characteristics of the study groups at randomization			
	Placebo (n = 25)	Liraglutide (n = 26)	P value
Demographic			
Age (years)	57.4 $\pm$ 7.4	58.9 $\pm$ 8.7	0.50
Male sex	64.0	61.5	0.86
Ethnicity			0.69
White	68.0	73.1	
Other	32.0	26.9	
Duration of diabetes (years)	1.5 (0.75–3.0)	3.0 (2.0–5.0)	0.028
Metabolic status			
BMI (kg/m ²)	30.4 $\pm$ 5.8	30.0 $\pm$ 4.3	0.82
Waist circumference (cm)	103.0 $\pm$ 13.7	99.8 $\pm$ 10.3	0.35
Fasting plasma glucose (mmol/L)	5.7 $\pm$ 0.5	5.9 $\pm$ 0.7	0.53
2-h glucose on OGTT (mmol/L)	13.3 $\pm$ 3.0	14.8 $\pm$ 2.8	0.07
AUC _{gluc} on OGTT	49.0 $\pm$ 4.8	50.3 $\pm$ 7.4	0.46
HbA _{1c} (%)	6.2 $\pm$ 0.4	6.4 $\pm$ 0.5	0.07
Insulin sensitivity/resistance			
Matsuda index	2.2 (1.6–3.8)	3.3 (2.1–5.5)	0.18
HOMA-IR	3.2 (1.8–4.9)	2.5 (1.3–4.1)	0.33
β -Cell function			
ISSI-2	220 (190–289)	193 (146–321)	0.34

The Liraglutide and Beta-cell RepAir (LIBRA) trial is a double-blind, randomized, parallel-arm, placebo-controlled trial designed to determine whether liraglutide can preserve β -cell function over 48 wks in earlyT2DM, following a short course of IIT (4 wks) prior to randomization



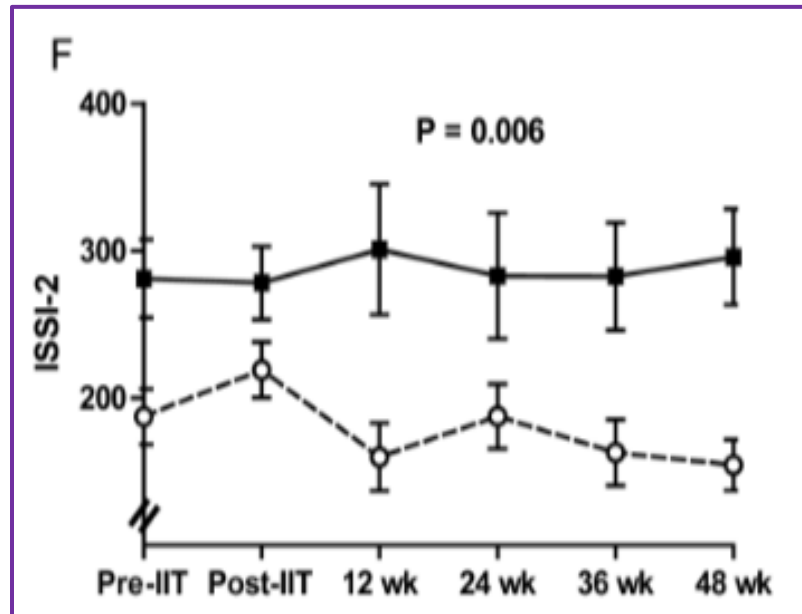
Nell' "early" DM2 il pre-trattamento insulinico intensivo non assicura il mantenimento a lungo termine degli effetti di liraglutide sulla funzione β cellulare

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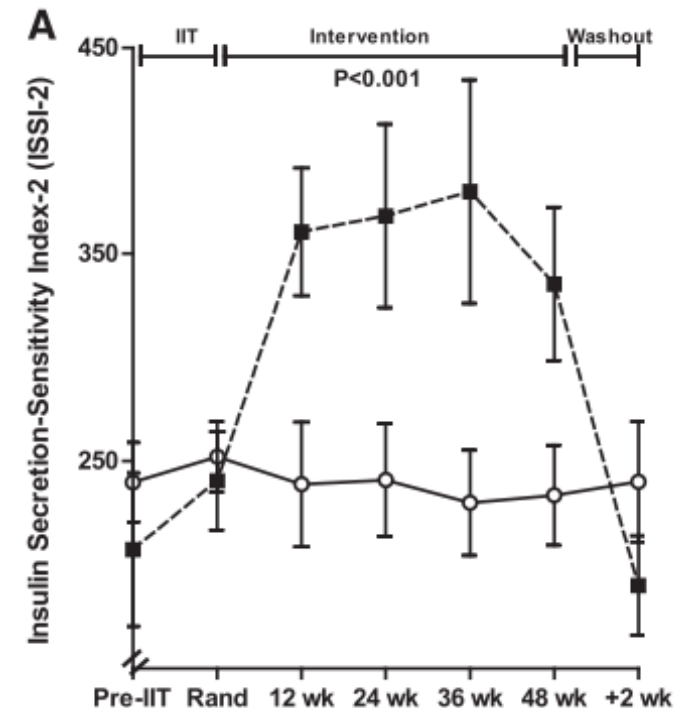
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GRUPPO PLACEBO



Remissione

Non remissione



Nell’ “early” DM2 l'aggiunta di exenatide all'insulina basale non migliora ulteriormente la funzione β cellulare o la capacità di raggiungere la remissione del diabete

nature communications

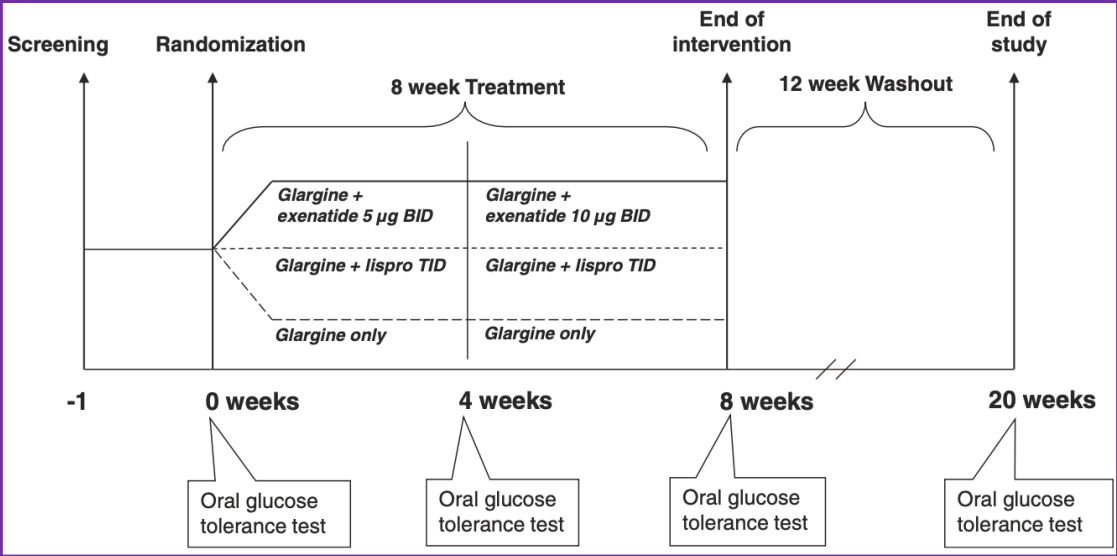


Article <https://doi.org/10.1038/s41467-022-33867-9>

The metabolic effects of adding exenatide to basal insulin therapy when targeting remission in early type 2 diabetes in a randomized clinical trial

Table 1 | Baseline characteristics of the three groups: (I) Glargine, (II) Glargine + Lispro, and (III) Glargine + Exenatide

	(Group I) Glargine (n = 33)	(Group II) Glargine + Lispro (n = 35)	(Group III) Glargine + Exenatide (n = 34)	Overall P
Age (years)	58 ± 10	59 ± 9	56 ± 10	0.40
Sex (% male)	19 (57.6)	16 (45.7)	23 (67.7)	0.18
Ethnicity:	–	–	–	0.65
White (%)	23 (69.7)	21 (60.0)	20 (58.8)	–
South Asian (%)	2 (6.1)	4 (11.4)	6 (17.7)	–
Other (%)	8 (24.2)	10 (28.6)	8 (23.5)	–
Duration of diabetes (years)	3.0 (1.9–5.5)	4.0 (1.9–5.8)	3.9 (1.5–5.3)	0.87
Weight (kg)	93.7 ± 18.1	88.9 ± 18.2	93.0 ± 23.3	0.56
Body mass index (kg/m ²)	32.3 ± 6.6	32.9 ± 8.4	31.7 ± 7.6	0.94
Waist circumference (cm)	108.4 ± 14.5	104.7 ± 15.0	107.0 ± 16.9	0.62
Glycemia:	–	–	–	–
A1c (%)	6.6 ± 0.7	6.5 ± 0.8	6.6 ± 0.6	0.83
A1c (mmol/mol)	48.8 ± 8.1	47.6 ± 9.0	48.3 ± 6.6	0.83
Fasting glucose (mmol/l)	7.1 ± 1.6	6.9 ± 1.5	7.0 ± 1.2	0.91
Insulin sensitivity/resistance:	–	–	–	–
Matsuda index	2.3 (1.8–3.1)	2.3 (1.2–3.8)	2.6 (1.6–4.1)	0.99
HOMA-IR	3.9 (3.3–6.7)	4.2 (2.6–9.0)	3.5 (2.3–7.3)	0.95
Beta-cell function:				
ISSI-2	195 (103–268)	171 (114–244)	192 (118–237)	0.89



Nell' "early" DM2 l'aggiunta di exenatide all'insulina basale non migliora ulteriormente la funzione β cellulare o la capacità di raggiungere la remissione del diabete

nature communications



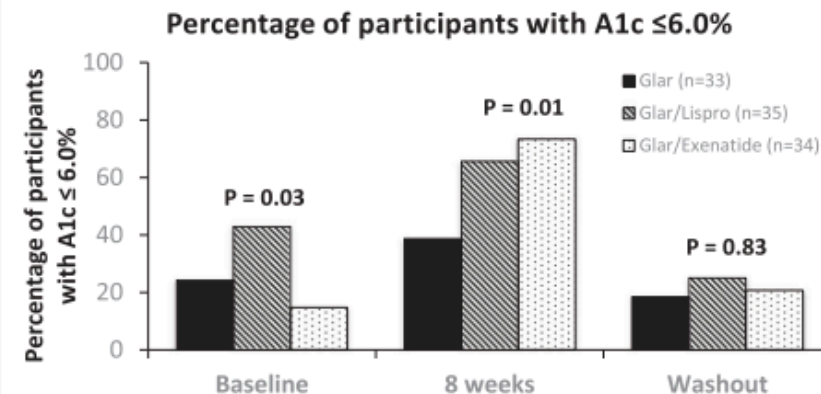
Article

<https://doi.org/10.1038/s41467-022-33867-9>

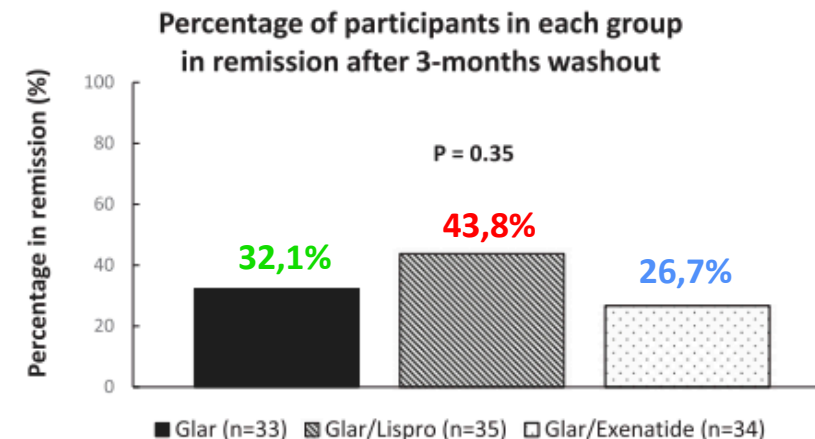
The metabolic effects of adding exenatide to basal insulin therapy when targeting remission in early type 2 diabetes in a randomized clinical trial

*«Despite its beneficial on-treatment effects on A1c and weight, the addition of exenatide to basal insulin in early T2DM did not further enhance underlying betacell function or the capacity to achieve diabetes remission. These findings are consistent with existing literature on **the absence of post therapy effects of GLP1-RAs in early T2DM.**»*

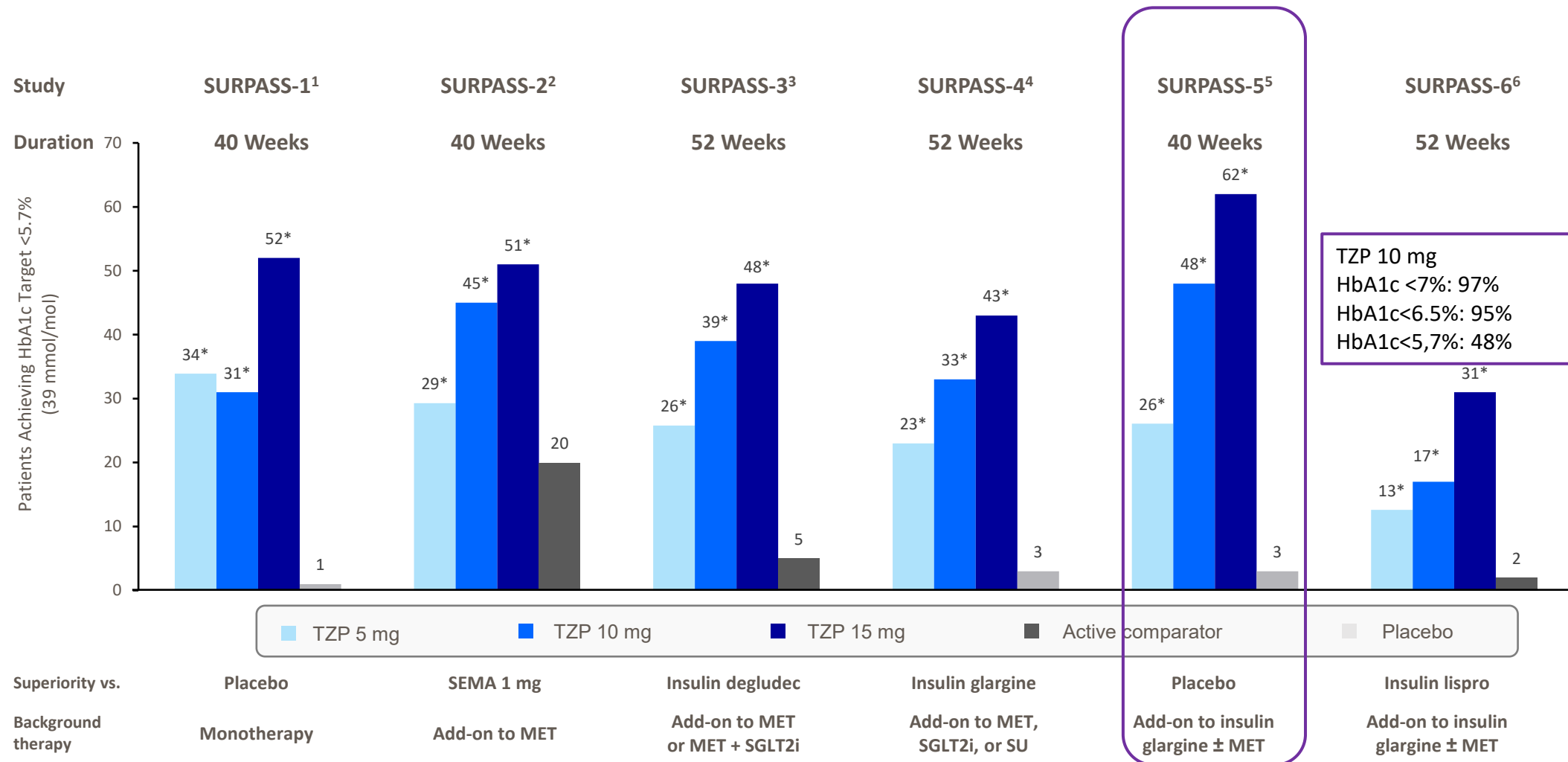
Panel A



Panel B



Quali aspettative possiamo avere per il doppio agonismo recettoriale GIP-GLP1?



1. Rosenstock J, et al. *Lancet*. 2021;398(10295):143-155. 2. Frias JP, et al. *N Eng J Med*. 2021;385(6):503-515. 3. Ludvik B, et al. *Lancet*. 2021;398(10300):583-598. 4. Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824. 5. Dahl D, et al. *JAMA*. 2022;327(6):534-545. 6. Rosenstock J, et al. Poster presented at: ADA 2023. Poster 750-P.

Quali aspettative possiamo avere per il doppio agonismo recettoriale GIP-GLP1?

The NEW ENGLAND JOURNAL of MEDICINE

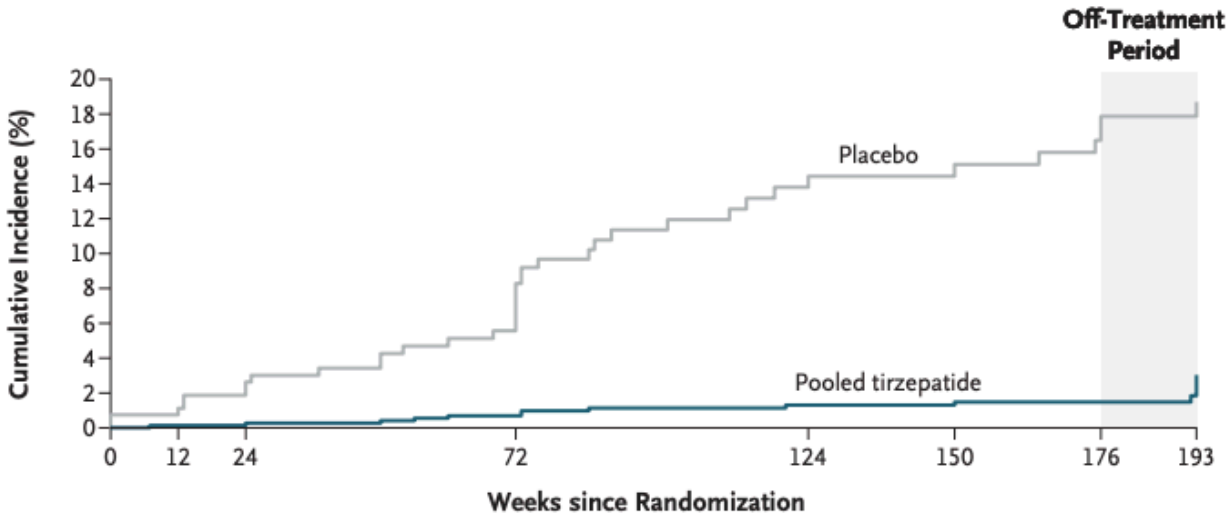
ORIGINAL ARTICLE

Tirzepatide for Obesity Treatment and Diabetes Prevention

Ania M. Jastreboff, M.D., Ph.D., Carel W. le Roux, F.R.C.P., Ph.D., Adam Stefanski, M.D., Ph.D., Louis J. Aronne, M.D., Bruno Halpern, M.D., Ph.D., Sean Wharton, M.D., Pharm.D., John P.H. Wilding, D.M., Leigh Perreault, M.D., Shuyu Zhang, M.S., Ramakrishna Battula, M.S., Mathijs C. Bunck, M.D., Ph.D., Nadia N. Ahmad, M.D., M.P.H., and Irina Jouravskaya, M.D., Ph.D., for the SURMOUNT-1 Investigators*

«Fewer participants received a diagnosis of type 2 diabetes in the tirzepatide groups than in the placebo group (1.3% vs. 13.3%; hazard ratio, 0.07; 95% confidence interval [CI], 0.0 to 0.1; $P<0.001$). After 17 weeks off treatment or placebo, 2.4% of the participants who received tirzepatide and 13.7% of those who received placebo had type 2 diabetes (hazard ratio, 0.12; 95% CI, 0.1 to 0.2; $P<0.001$).»

C Incidence of Type 2 Diabetes



No. at Risk							
Placebo	270	266	257	209	137	126	121
Pooled tirzepatide	762	751	742	700	581	570	557
No. of Participants with Diagnosis							
Placebo	2	3	7	20	31	32	36
Pooled tirzepatide	0	1	2	5	9	10	10

Conclusioni

- ❑ La terapia insulinica intensiva a breve termine è tuttora l'unica terapia farmacologica di dimostrata efficacia nell'indurre una remissione del DM2 secondo i criteri della Consensus del 2021
- ❑ La terapia insulinica intensiva può migliorare la fisiopatologia nelle fasi precoci di malattia e quindi essere una delle strategie di trattamento per modificare la storia naturale del diabete
- ❑ L'associazione sequenziale con i promettenti farmaci incretino-mimetici potrebbe essere un ambito clinico da esplorare nei prossimi anni