CONGRESSO REGIONALE
SID-AMD
LAZIO
DIABETOLOGIA 2024:
NUOVI SCENARI CLINICI
E PROSPETTIVE TERAPEUTICHE

# CLINICAL DEBATE - REMISSIONE DEL DIABETE TIPO 2
## Terapia farmacologica


**DANILA FAVA**

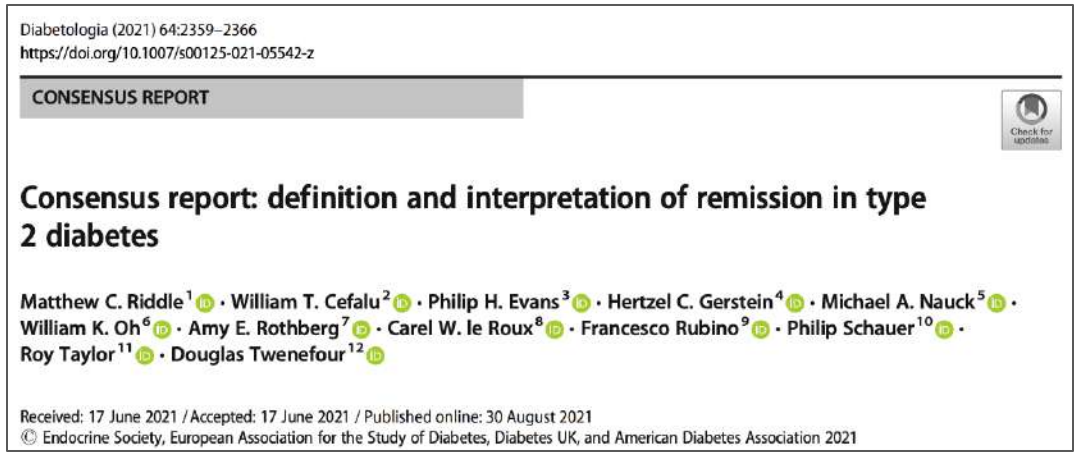
*UOSD Endocrinologia e Diabetologia*

*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
- Movi
- 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

Matthew C. Riddle[1] · William T. Cefalu[2] · Philip H. Evans[3] · Hertzel C. Gerstein[4] · Michael A. Nauck[5] · William K. Oh[6] · Amy E. Rothberg[7] · Carel W. le Roux[8] · Francesco Rubino[9] · Philip Schauer[10] · Roy Taylor[11] · Douglas Twenefour[12]

Received: 17 June 2021 / Accepted: 17 June 2021 / Published online: 30 August 2021


**« 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 »**

*Riddle MC et al, Diabetologia 2021*

# Remissione nel diabete tipo 2: quali interventi per ottenerla?

**Table 1—Interventions and temporal factors in determining remission of T2D**

| Intervention<br>*Note: Documentation of remission should include a measurement of $HbA_{1c}$ just prior to intervention* | 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 after cessation of this intervention | Not more often than every 3 months nor less frequent than yearly |
| Surgery | At least 3 months after the procedure *and* 3 months after cessation of any pharmacotherapy | |
| Lifestyle | At least 6 months after beginning this intervention *and* 3 months after cessation of any pharmacotherapy | |

Interruzione dell'intervento

La chirurgia bariatrica è un trattamento permanente

Lo stile di vita salutare viene mantenuto

*Riddle MC et al, Diabetologia 2021*

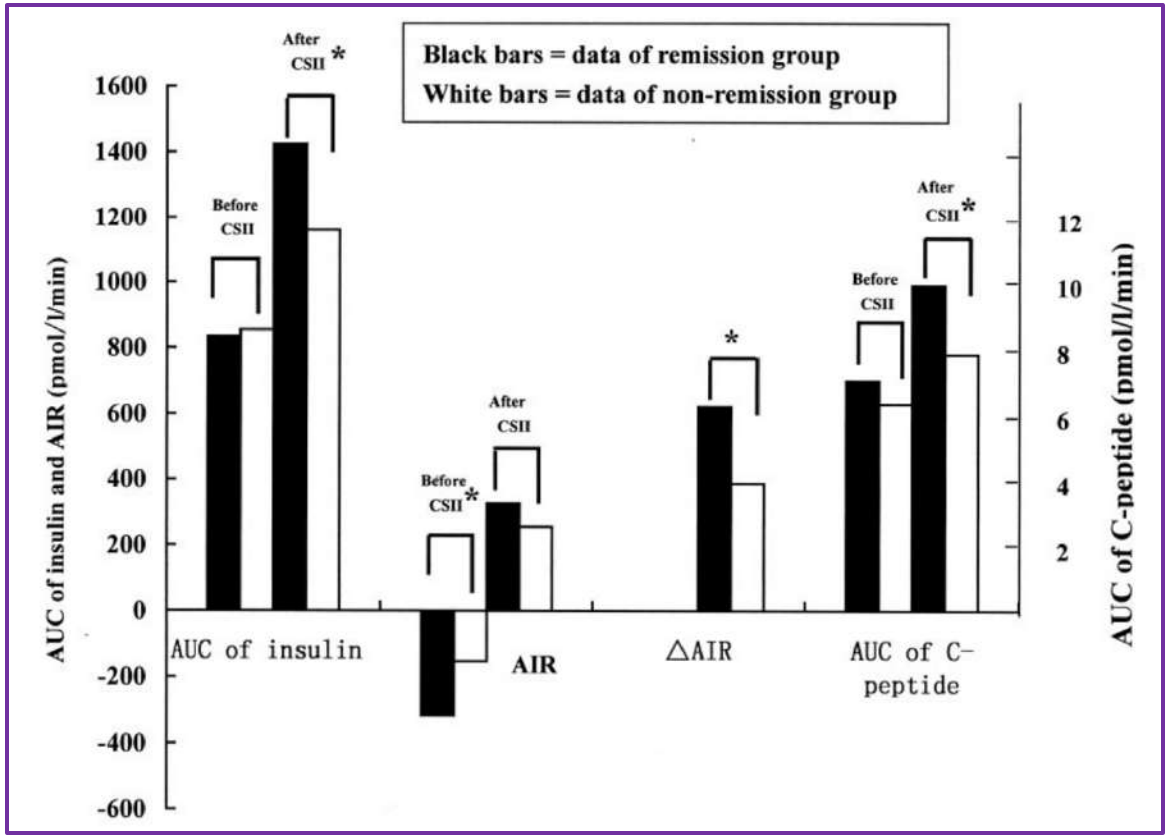
# La terapia insulinica intensiva a breve termine nel DM2 di nuova diagnosi è associata al miglioramento della funzione β cellulare a lungo termine

**Table 2—*Clinical characteristics in the remission and nonremission groups***

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

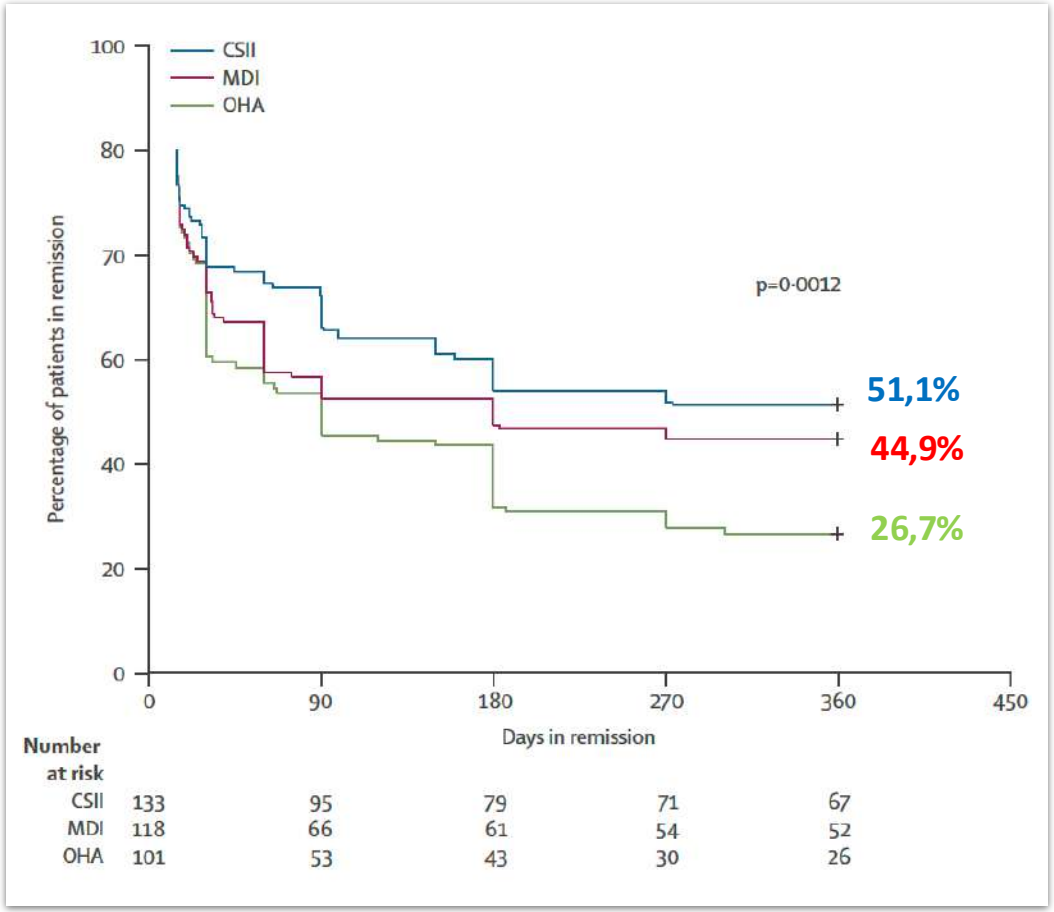
**Soggetti in remissione:**

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




LI Y et al, *Diabetes Care 2004*

# 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*

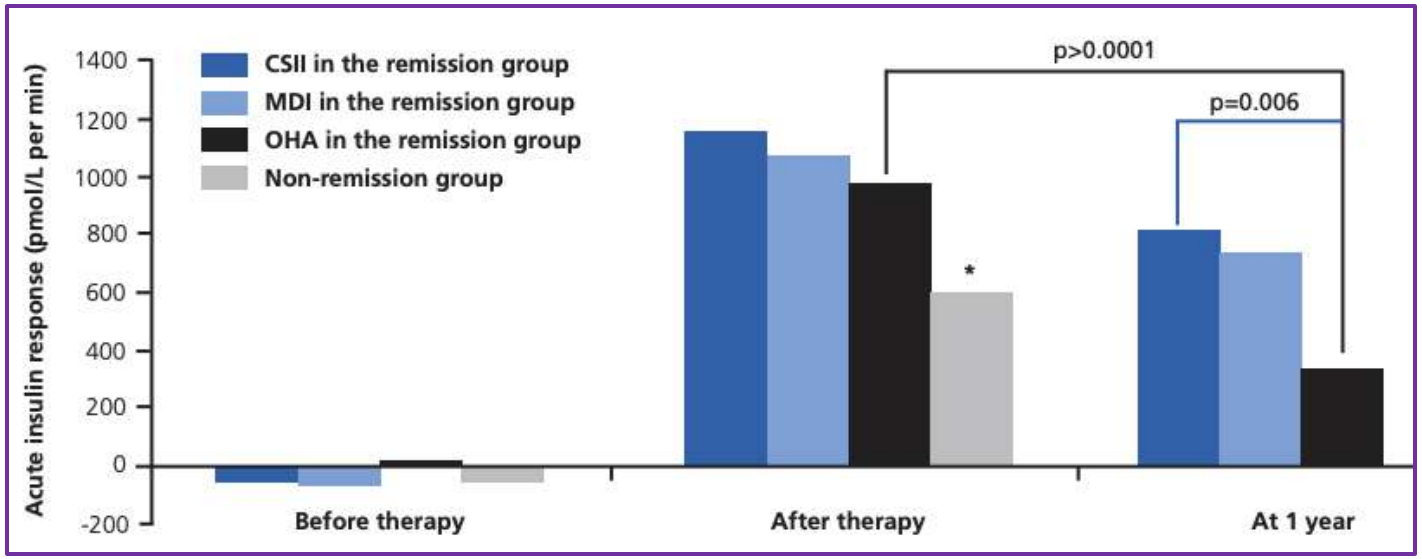
| | |
|---|---|
| Glycaemic goals: | FPG: <110 mg/dl<br>2-hr after each meal: <144 mg/dl |
| Treatment: | maintained for 2 weeks after reaching glycemic targets |
| Remission: | optimum glycemic control ≥ 12 months without medication |
| Non-remission: | FPG > 126 mg/dl or<br>2-hr pp glucose > 180 mg/dl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

Weng J et al, *Lancet* 2008

# 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) |

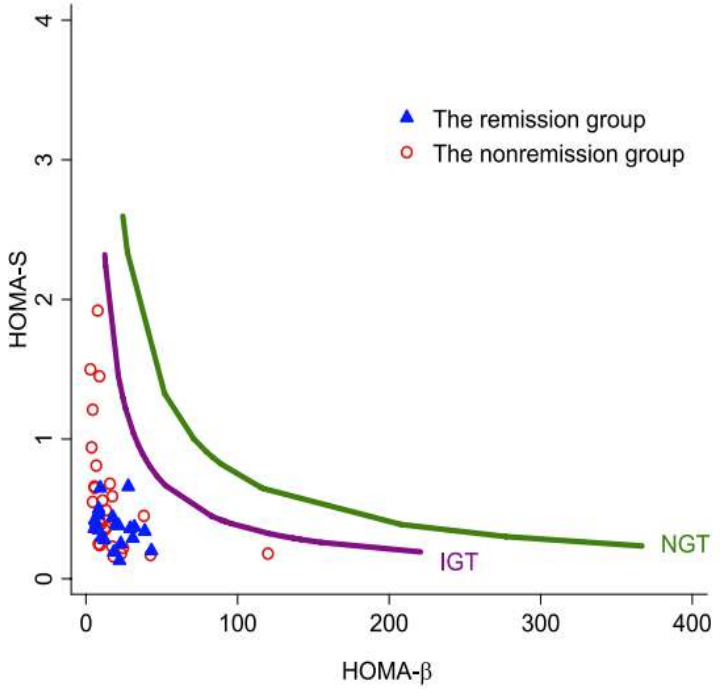
Data are mean (SD) unless otherwise indicated. *p<0·0001 compared with before treatment. †Data are median (IQR). ‡p<0·05 compared with CSII.



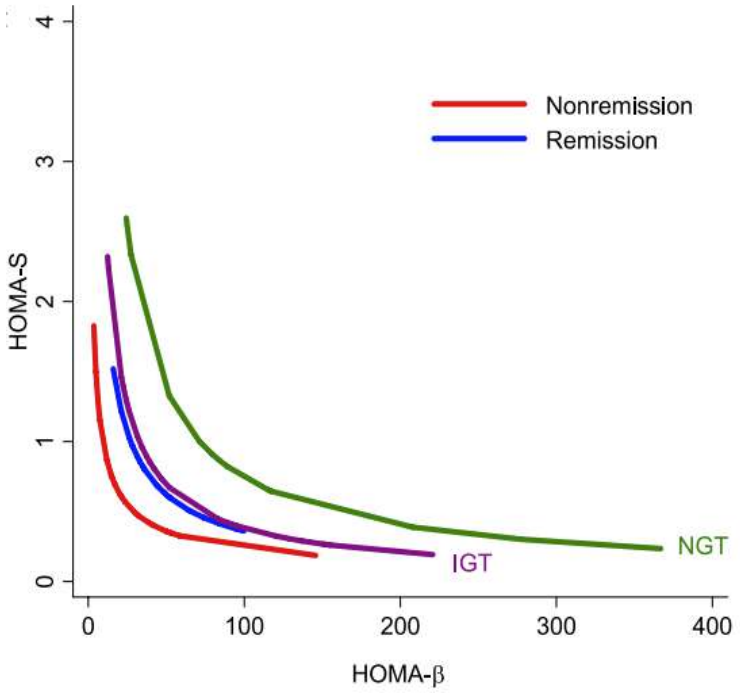

Weng J et al, *Lancet* 2008

# 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

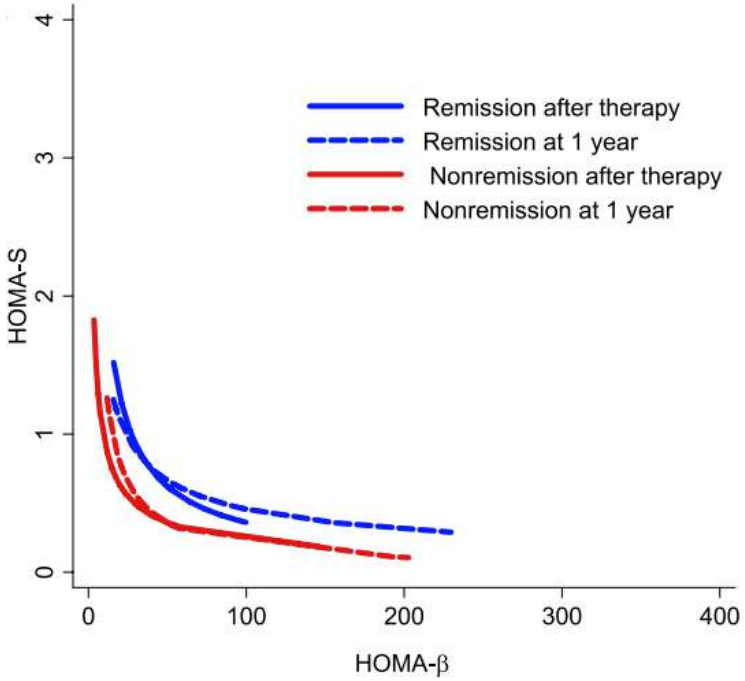
*Before therapy*




*After 2 weeks*

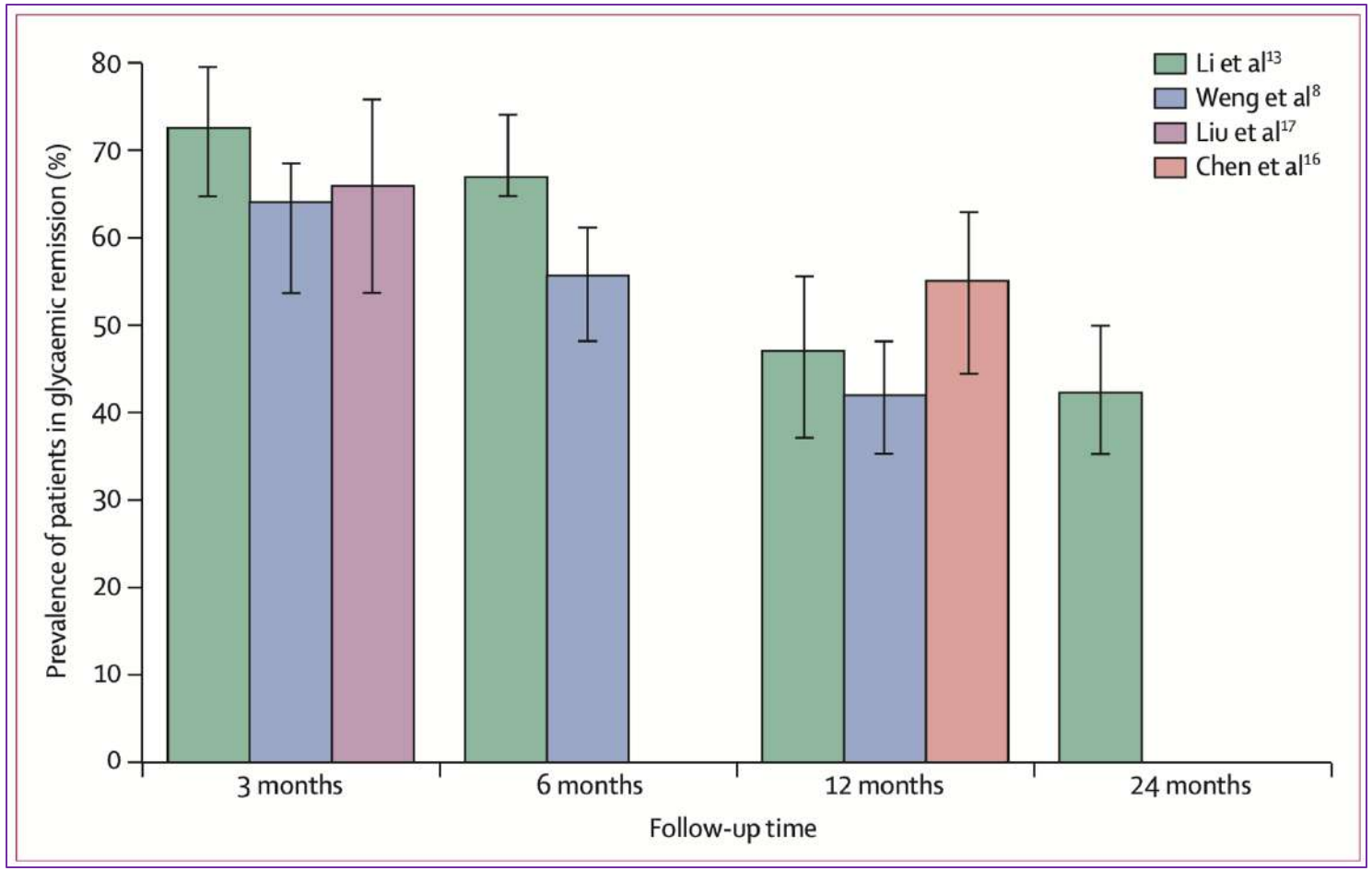



*After 1 year*




Yun H et al, *Diabetes Care 2011*

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




Kramer CK et al, *Lancet Diabetes Endocrinol* 2013

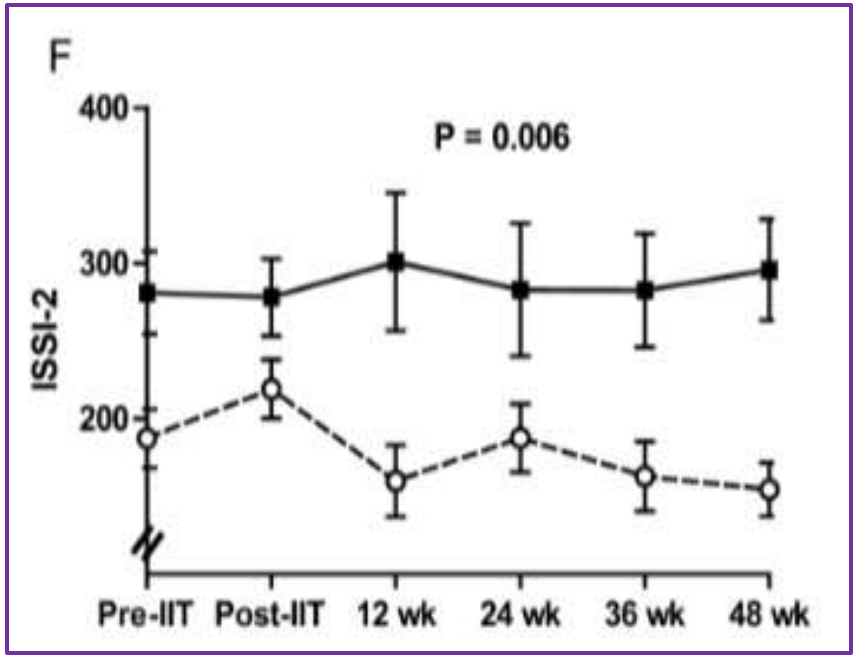
# Nell' "early" DM2 la probabilità di remissione dopo terapia insulinica intensiva correla con la durata di malattia ed il valore di HbA1c

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) * |




Remissione

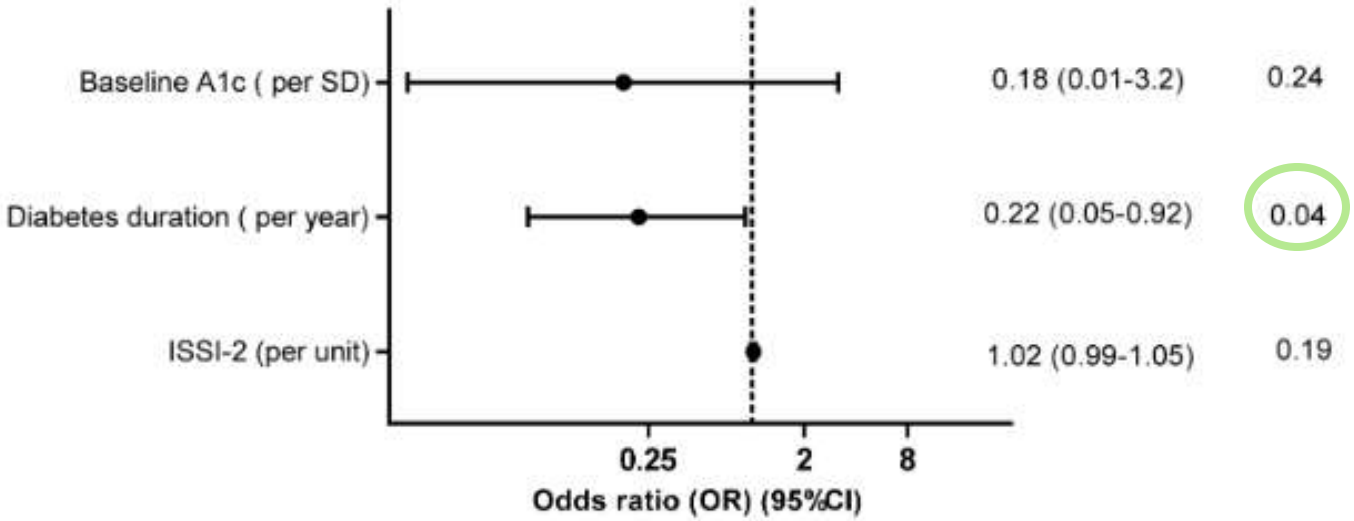
Non remissione

**Andamento di ISSI-2 nei 2 gruppi**

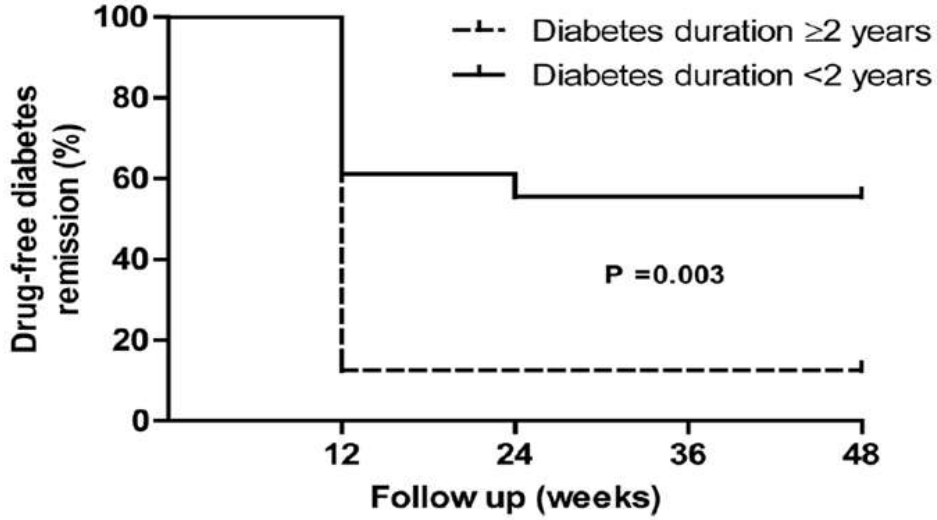
Kramer CK et al, *BMJ Open Diabetes Res Care* 2016

# 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**




Kramer CK et al, *BMJ Open Diabetes Res Care* 2016

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

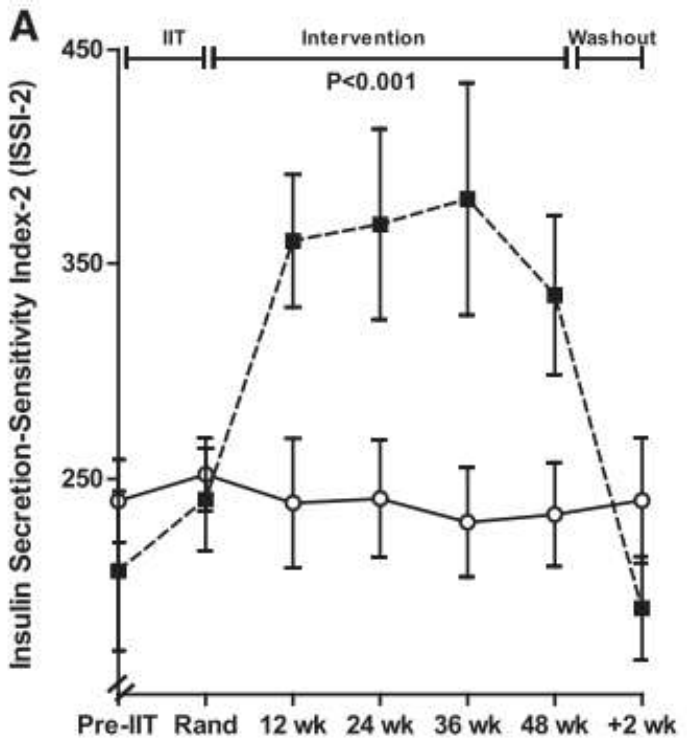
## Liraglutide and the Preservation of Pancreatic β-Cell Function in Early Type 2 Diabetes: The LIBRA Trial

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

*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 ß-cell function over 48 wks in earlyT2DM, following a short course of IIT (4 wks) prior to randomization*

**Table 1—Baseline characteristics of the study groups at randomization**

| | Placebo ($n$ = 25) | Liraglutide ($n$ = 26) | $P$ value |
|---|---|---|---|
| Demographic | | | |
| Age (years) | 57.4 ± 7.4 | 58.9 ± 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 ± 5.8 | 30.0 ± 4.3 | 0.82 |
| Waist circumference (cm) | 103.0 ± 13.7 | 99.8 ± 10.3 | 0.35 |
| Fasting plasma glucose (mmol/L) | 5.7 ± 0.5 | 5.9 ± 0.7 | 0.53 |
| 2-h glucose on OGTT (mmol/L) | 13.3 ± 3.0 | 14.8 ± 2.8 | 0.07 |
| $AUC_{gluc}$ on OGTT | 49.0 ± 4.8 | 50.3 ± 7.4 | 0.46 |
| $HbA_{1c}$ (%) | 6.2 ± 0.4 | 6.4 ± 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 |




Retnakaran R et al, *Diabetes Care 2014*

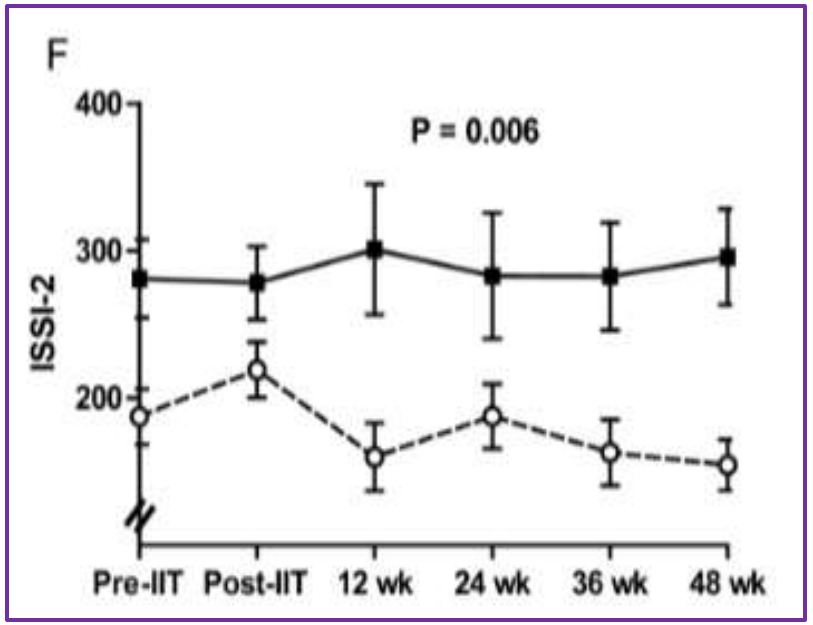
# Nell' "early" DM2 il pre-trattamento insulinico intensivo non assicura il mantenimento a lungo termine degli effetti di liraglutide sulla funzione β cellulare

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*

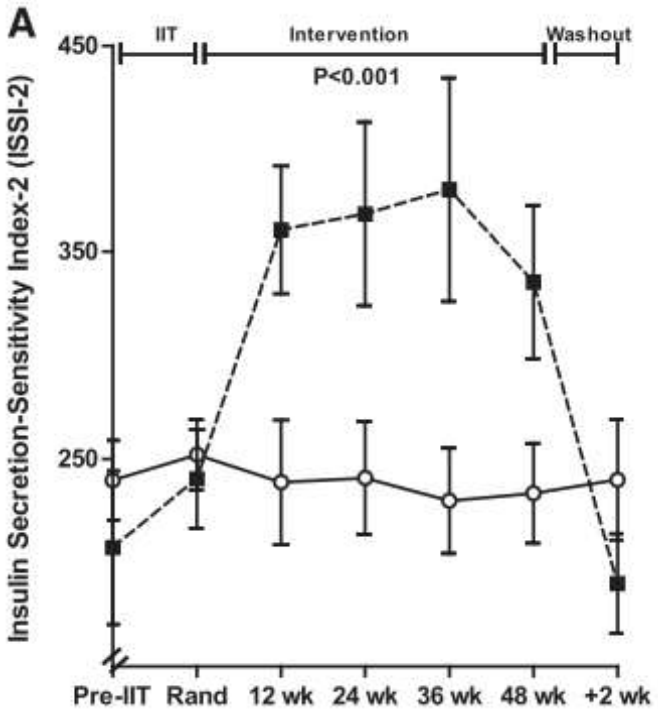
*The LIraglutide and Beta-cell RepAir (LIBRA) trial is a double-blind, randomized, parallel-arm, placebo-controlled trial designed to determine whether liraglutide can preserve β-cell function over 48 wks in earlyT2DM, following a short course of IIT (4 wks) prior to randomization*

GRUPPO PLACEBO




Remissione

Non remissione




Retnakaran R et al, *Diabetes Care 2014*

# 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

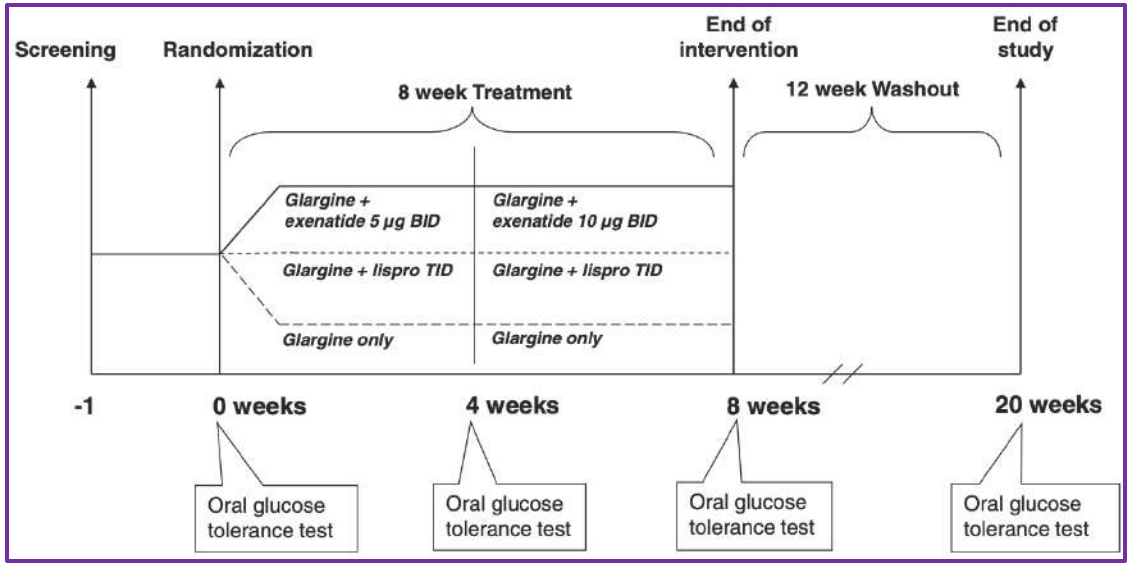
nature communications

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 |




Retnarakan R et al, *Nature Communications 2022*

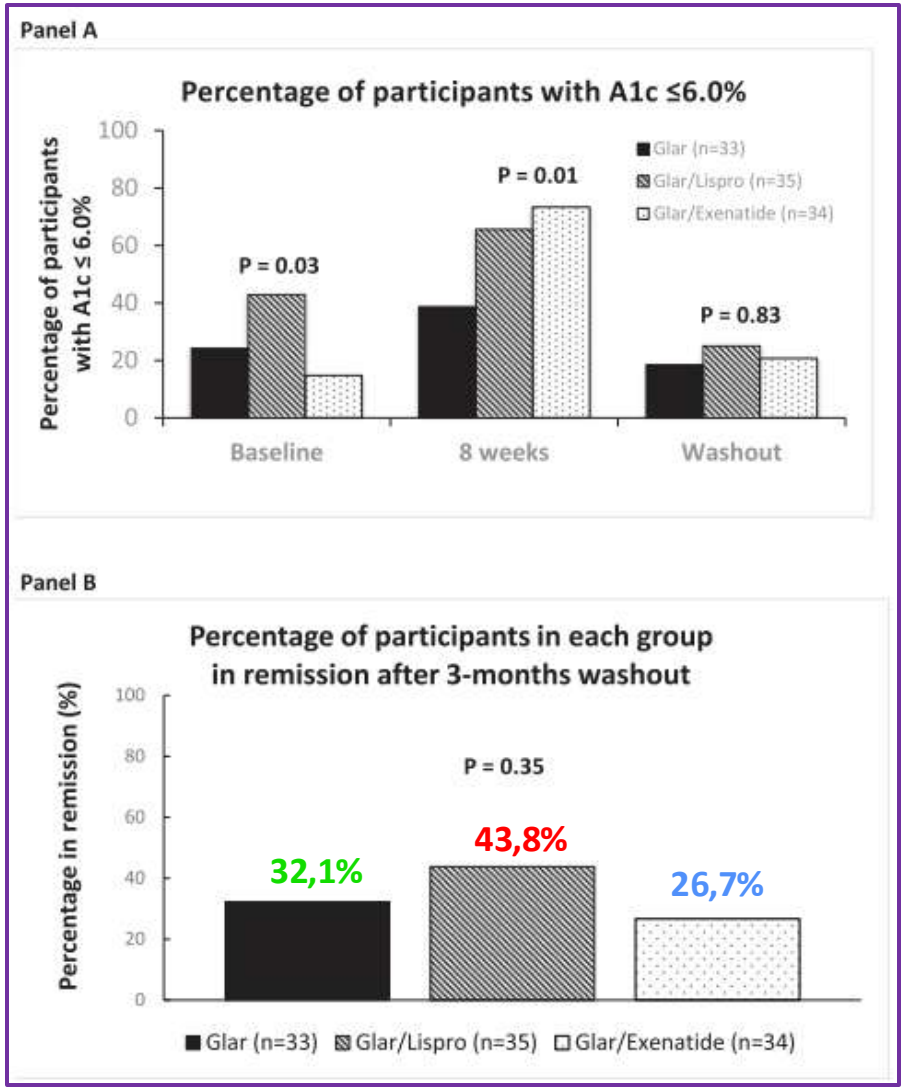
# Nell' "early" DM2 l'aggiunta di exenatide all'insulina basale non migliora ulteriormente la funzione β cellulare o la capacità di raggiungere la remissione del diabete

nature communications

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

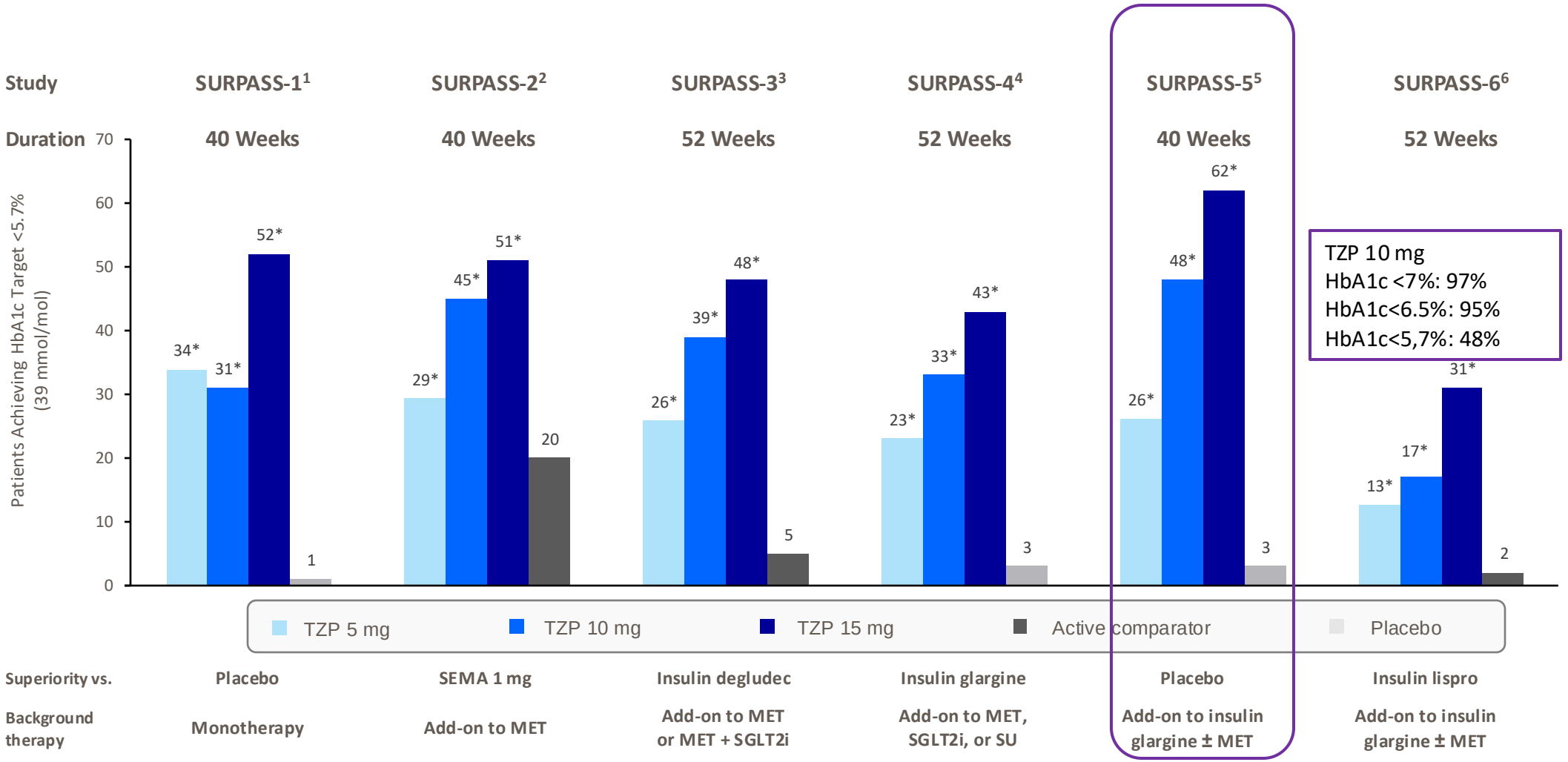
**The metabolic effects of adding exenatide to basal insulin therapy when targeting remission in early type 2 diabetes in a randomized clinical trial**

*«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.»***




Retnarakan R et al, *Nature Communications 2022*

# 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

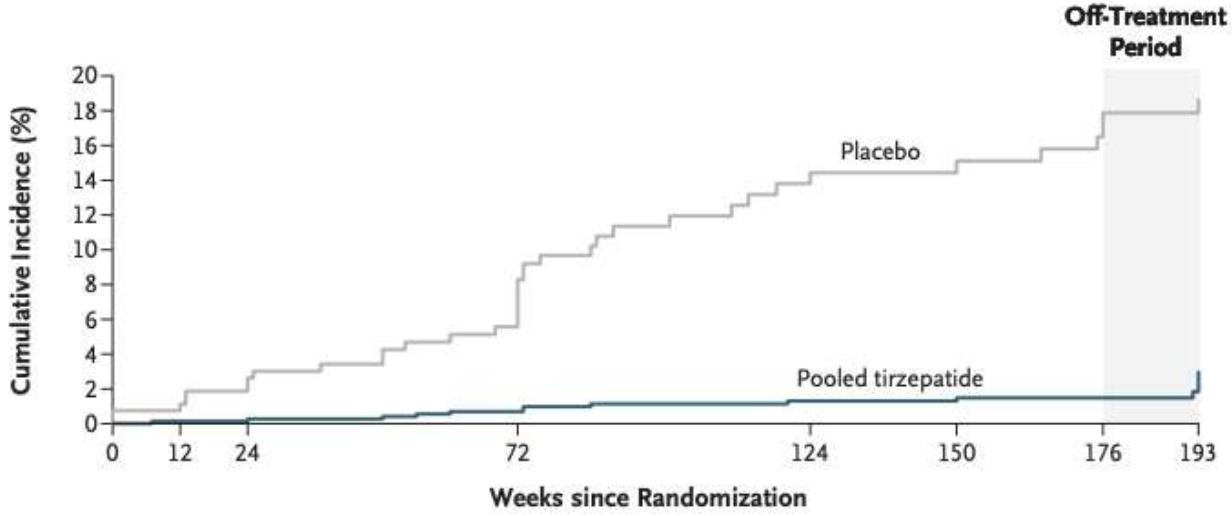
ORIGINAL ARTICLE

## 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 | 99 |
| Pooled tirzepatide | 762 | 751 | 742 | 700 | 581 | 570 | 557 | 494 |
| **No. of Participants with Diagnosis** | | | | | | | | |
| Placebo | 2 | 3 | 7 | 20 | 31 | 32 | 36 | 37 |
| Pooled tirzepatide | 0 | 1 | 2 | 5 | 9 | 10 | 10 | 18 |

Jastreboff AM et al, N Engl J Med 2024

# 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