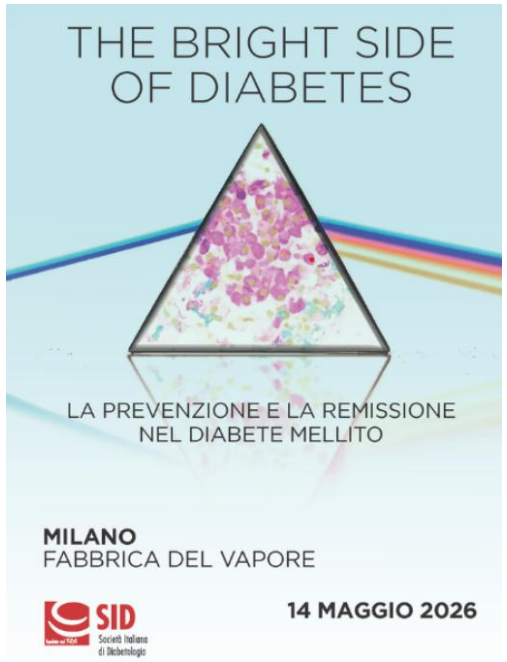
LA REMISSIONE FARMACOLOGICA E NON NEL T2D:

Associazione GLP1-RA, SGLT2-i e Dual Agonist-Tirzepatide



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Disclosures

Dichiaro di non avere conflitti d'interesse relativi alle tematiche presentate in questa relazione

Outline

- The concept of remission
- Achieving pharmacological remission in T2DM
- How to target pharmacological remission
- Conclusions

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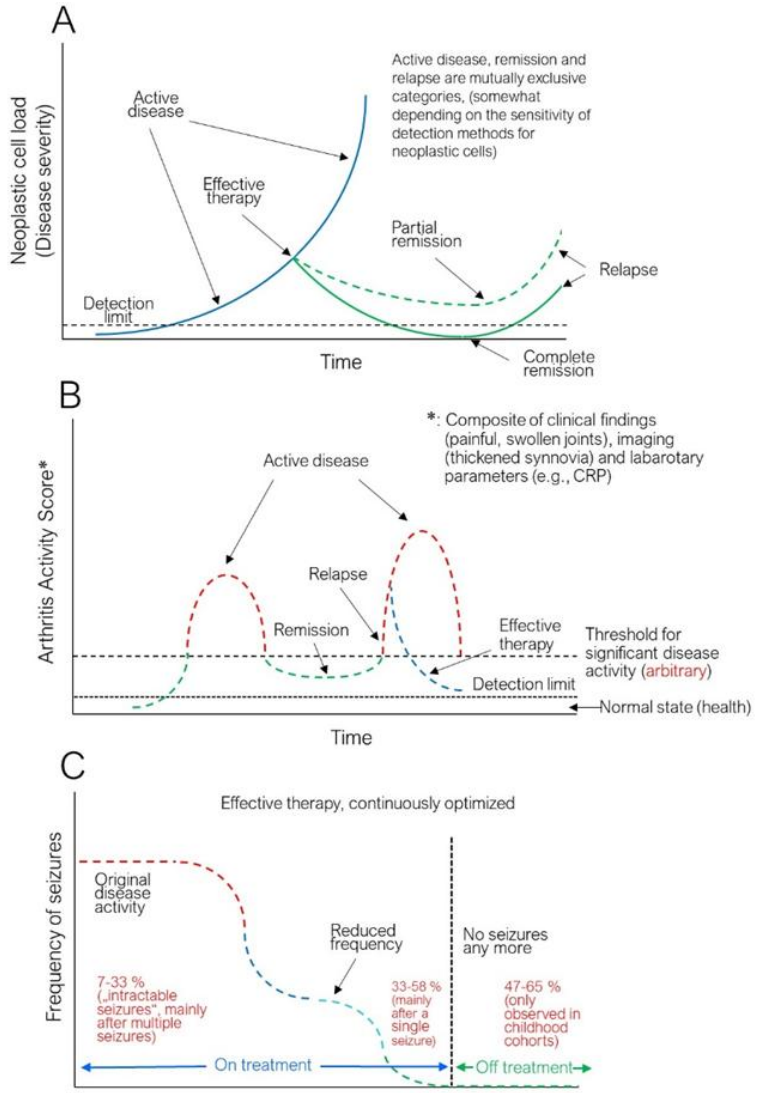
The concept of diabetes remission

“Remission should be defined as a return of HbA1c to <6,5%(<48 mmol/mol) 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. Diabet Med. 2022 Mar;39(3):e14669.

The concept of diabetes remission: should it differs from other diseases?



Definition of remission in other diseases

- Cancer → undetectable n° of neoplastic cells
- Rheumatoid arthritis → no clinical, imaging and laboratory finds of diseases
- Epilepsy → absence of seizures

With ongoing therapy

C. Bianchi et al Diabetes, Obesity and Metabolism, no. 6 (2026): 4474–4487,

The concept of diabetes remission: should it differs from other diseases?

"Nonetheless, it appears reasonable, if not necessary, to add a ***novel category of diabetes remission for people achieving this ambitious goal while taking glucose-and weight-lowering medications****. Such a category parallels and* ***aligns with the mechanisms driving glycaemic control and weight loss after bariatric surgery****, the origin of which the definition of T2DM remission comes, and reflects other commonly accepted definitions used outside the field of diabetes, including cancer, rheumatology and neurology. Furthermore, the* ***cardio-reno-protective properties of new glucose-and weight-lowering medications*** *in patients with type 2 diabetes and comorbidities, and their importance in preventing cardiovascular risk, cast* ***doubt on the appropriateness of discontinuing these drugs****"*

C. Bianchi et al Diabetes, Obesity and Metabolism, no. 6 (2026): 4474–4487,

The concept of diabetes remission

Definition 1

HbA1c <6,5% for at least 3 months without any therapy

Definition 2

HbA1c <6,5% for at least 3 months without any therapy other than GLP-1RA

Definition 3

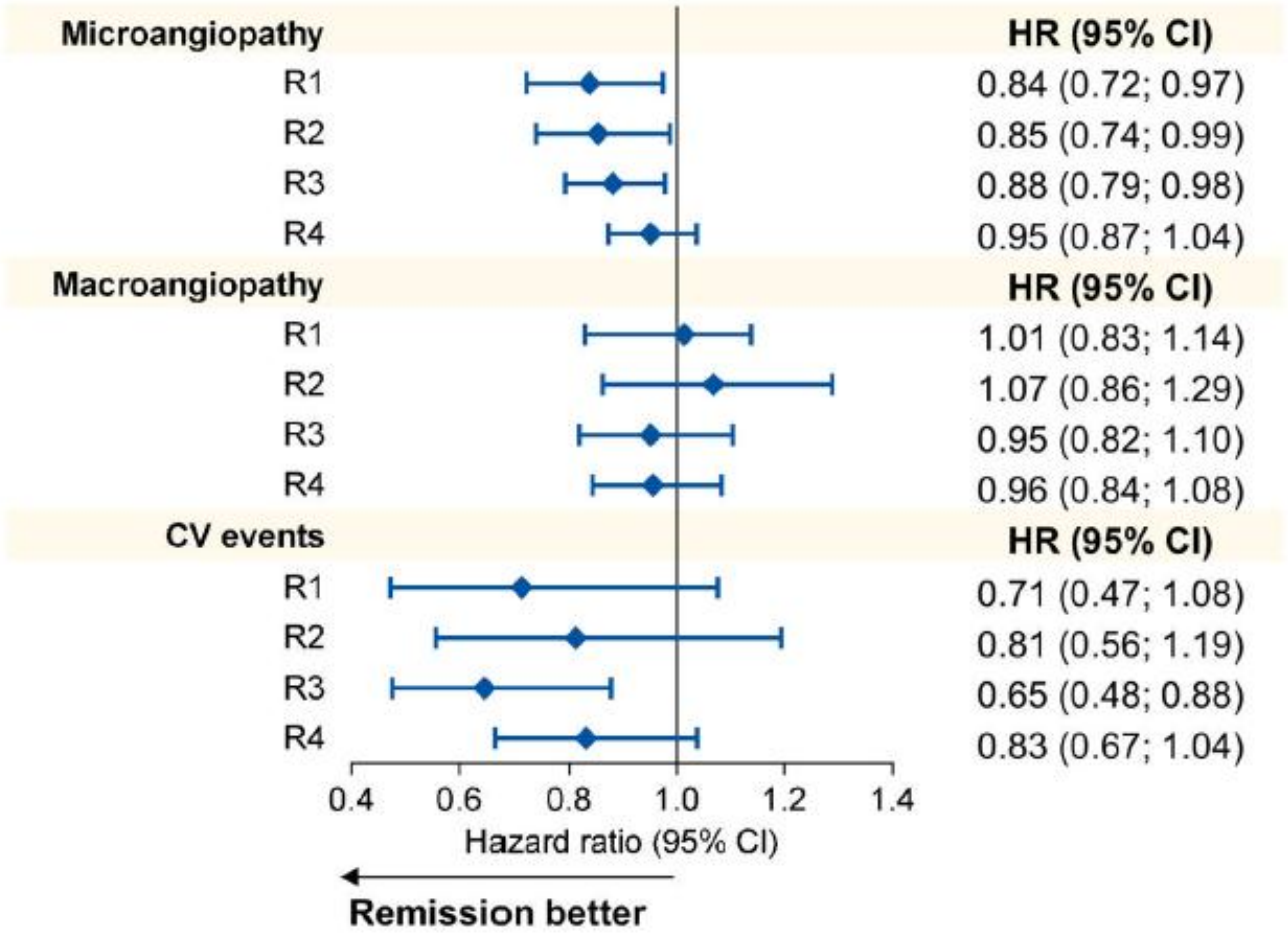
HbA1c <6,5% for at least 3 months without adding any new glucose-lowering medications from baseline

Definition 4

HbA1c <6,5% for at least 3 months irrespective of glucose-lowering medications

Fadini GP at al Lancet Reg Health Eur. 2025 Oct 15;59:101499.

The concept of diabetes remission



Fadini GP at al Lancet Reg Health Eur. 2025 Oct 15;59:101499.

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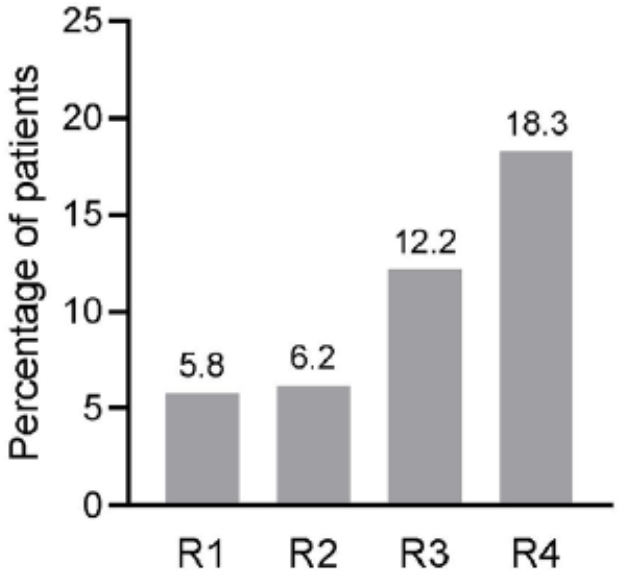
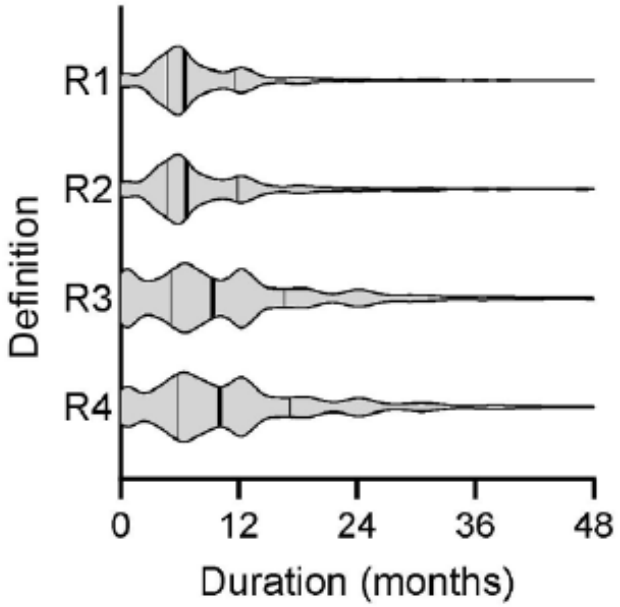
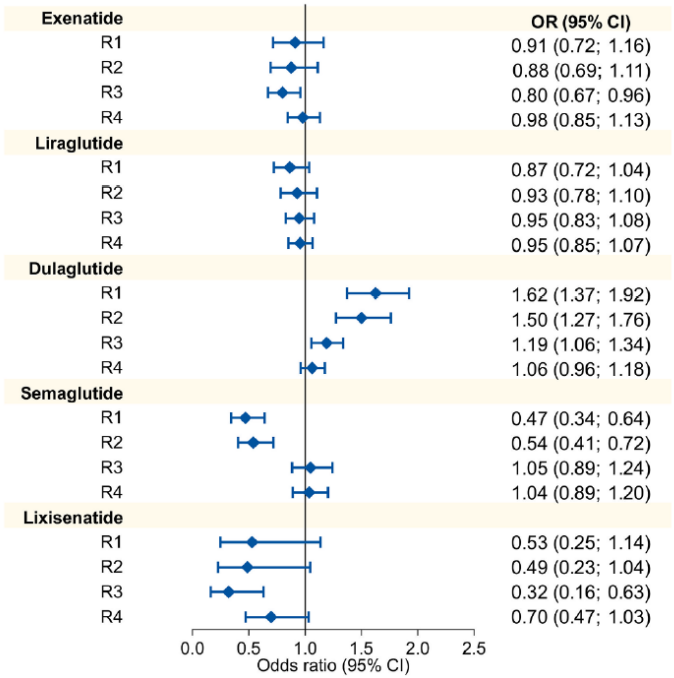
Achieving different definitions of remission through GLP-1RA



% of remission by definition



Mean duration of remission by definition

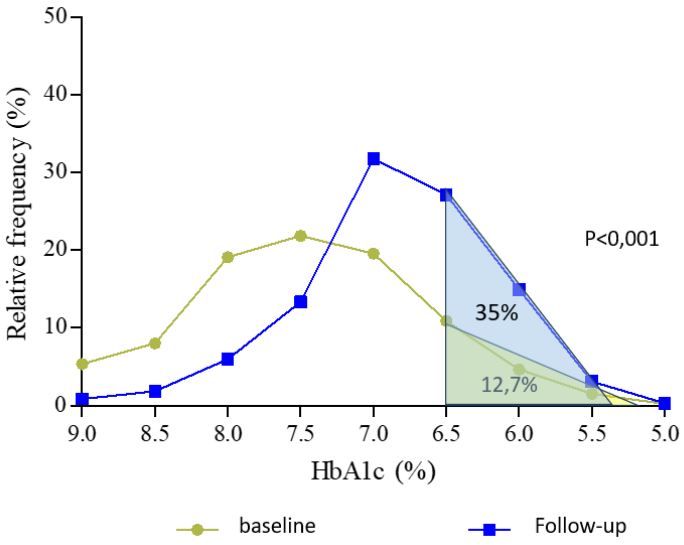


OR with each GLP-1RA by definition

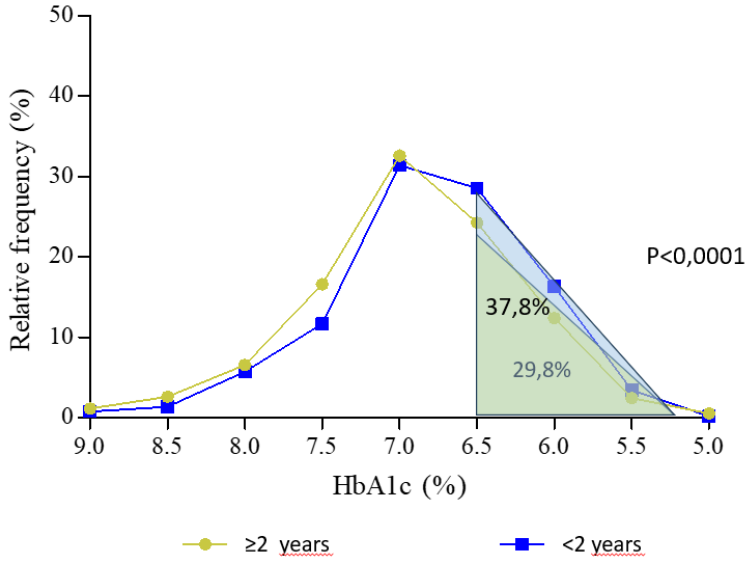
Fadini GP at al Lancet Reg Health Eur. 2025 Oct 15;59:101499.

Pharmacological remission with early introduction of SGLT2i

Overall Data



Comparison by diabetes duration

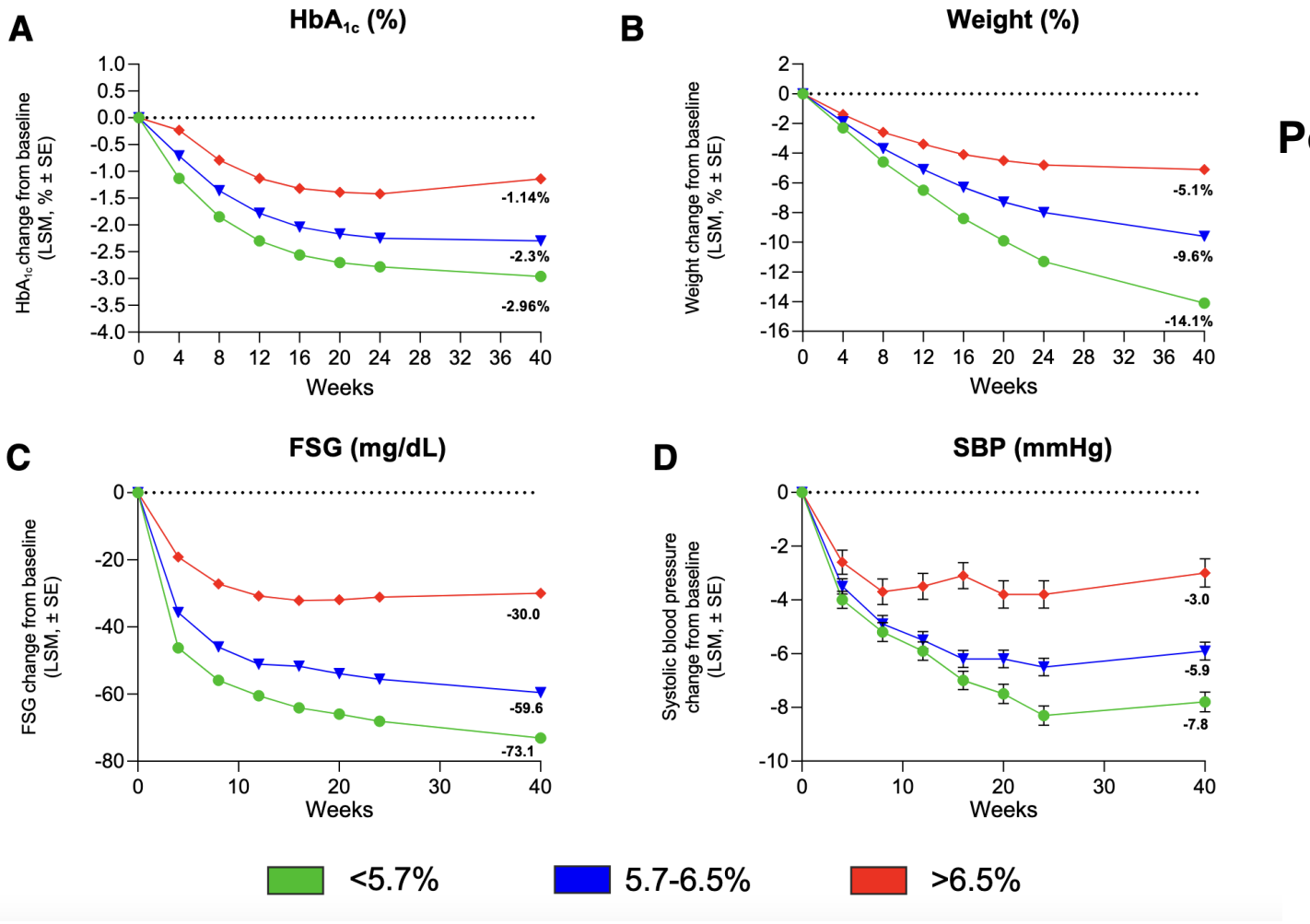


- Multi-center real world study
- n= 5294 patients enrolled
- Dapa start before vs after 2 years from diagnosis

- 35% remission Dapa vs 12,7% no Dapa
- Early introduction gives is more beneficial

Lunati ME, Bernasconi D et al Unpublished

Achievement of normoglycemia with tirzepatide: analysis of SURPASS 1-4

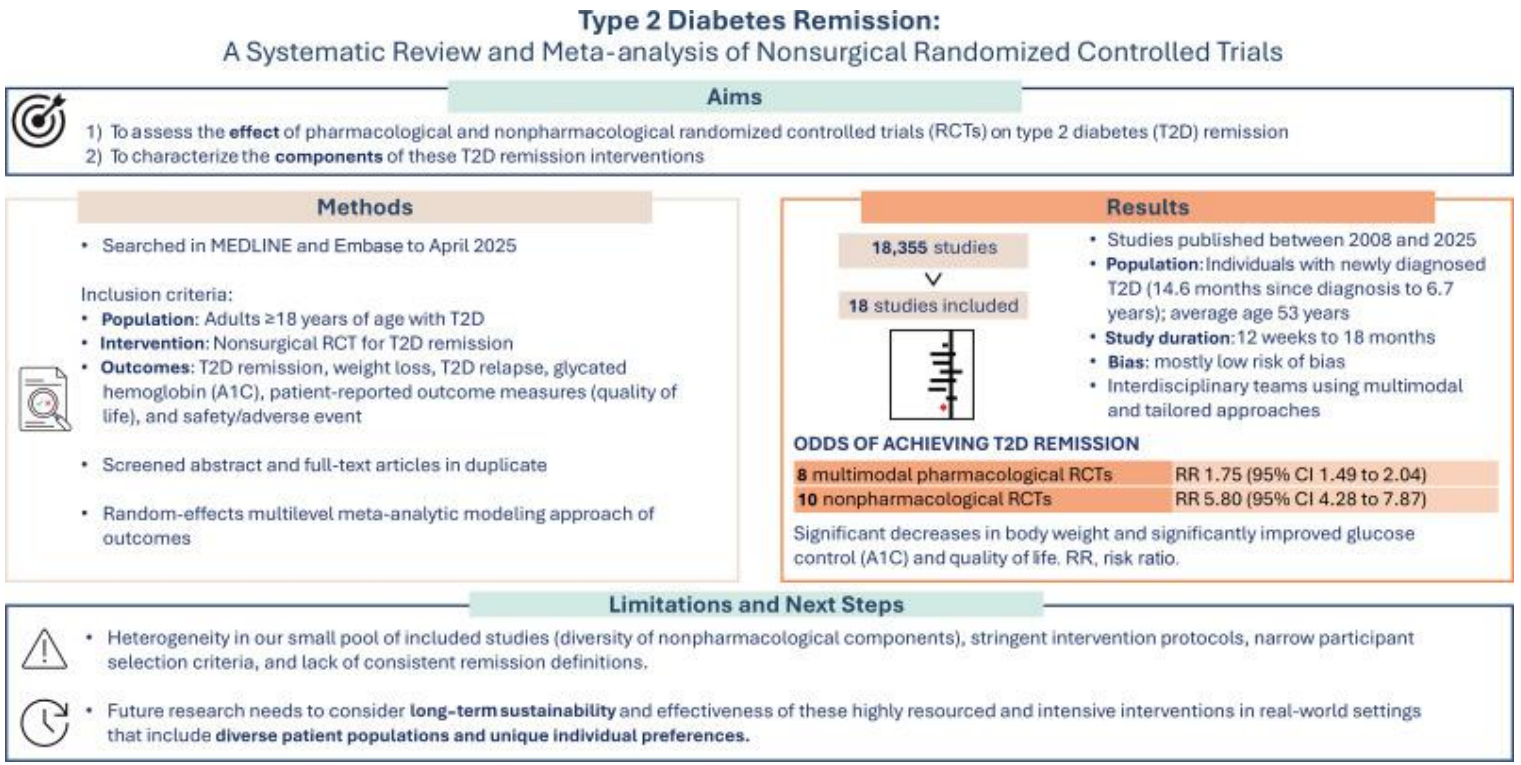


Post-hoc analysis of SURPASS 1-4

43 - 62% of participants treated with the highest tirzepatide dose (15 mg) achieved HbA1c <5.7% at the primary end point of each SURPASS study

Rosenstock J et al Diabetes Care. 2023 Nov 1;46(11):1986-1992.

Remission with multimodal pharmacotherapy



- 8 RCT with pharmacotherapy
- Only 2 included GLP-1RA
- Only 2 included SGLT2i
- No RCT with GLP-1RA and SGLT2i combination
- No consistent definition of remission

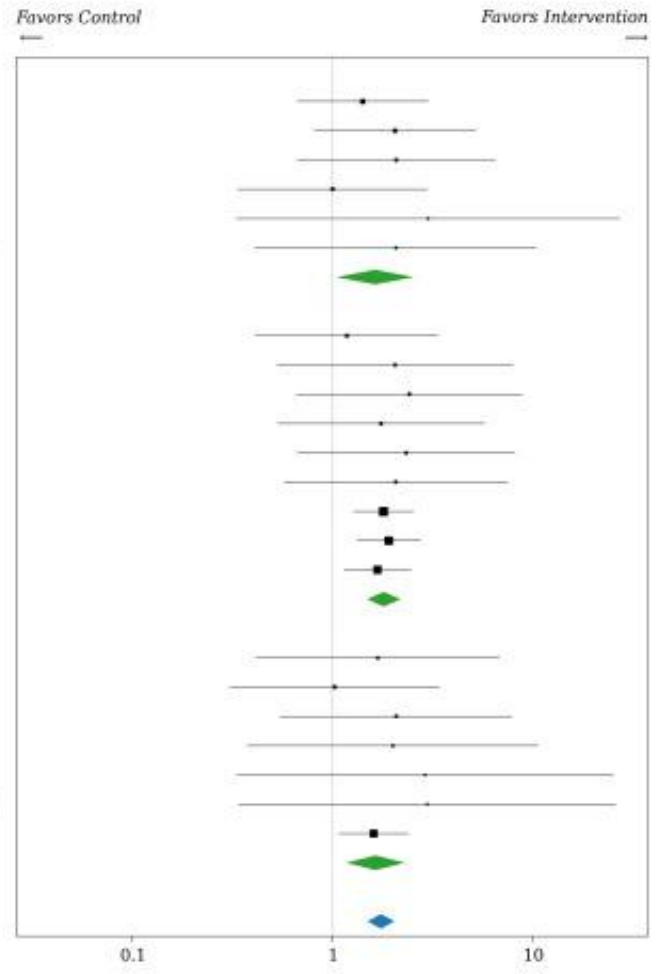
Sherifali DT et al Diabetes Care. 2025 Dec 1;48(12):2181-2191.

Remission with multimodal pharmacotherapy

A

Study	Intervention	(%)	Control	(%)	Weight	RR [95% CI]
Follow-up: ≤6 months						
Punthakee 2024	14/79	(17.7%)	10/80	(12.5%)	4.3%	1.42 [0.67, 3.0]
McInnes 2023	12/79	(15.2%)	6/81	(7.4%)	2.8%	2.05 [0.81, 5.2]
McInnes 2022	8/50	(16.0%)	4/52	(7.7%)	1.9%	2.08 [0.67, 6.48]
McInnes 2020	6/77	(7.8%)	6/77	(7.8%)	2.1%	1.0 [0.34, 2.96]
McInnes 2017-A	3/28	(10.7%)	1/28	(3.6%)	0.5%	3.0 [0.33, 27.12]
McInnes 2017-B	4/27	(14.8%)	2/28	(7.1%)	0.9%	2.07 [0.41, 10.41]
Subgroup Estimate	47/340	(13.8%)	29/346	(8.4%)	I^2: 0%	1.63 [1.05, 2.54]
Follow-up: >6 to 12 months						
Punthakee 2024	7/79	(8.9%)	6/80	(7.5%)	2.2%	1.18 [0.42, 3.36]
McInnes 2023	6/79	(7.6%)	3/81	(3.7%)	1.3%	2.05 [0.53, 7.92]
McInnes 2022	7/50	(14.0%)	3/52	(5.8%)	1.4%	2.43 [0.66, 8.87]
McInnes 2020	7/77	(9.1%)	4/77	(5.2%)	1.7%	1.75 [0.53, 5.74]
McInnes 2017-A	7/28	(25.0%)	3/28	(10.7%)	1.6%	2.33 [0.67, 8.12]
McInnes 2017-B	6/27	(22.2%)	3/28	(10.7%)	1.5%	2.07 [0.58, 7.47]
Shi 2017	47/66	(71.2%)	25/63	(39.7%)	20.9%	1.79 [1.28, 2.52]
Weng 2008-A	68/133	(51.1%)	27/101	(26.7%)	18.4%	1.91 [1.33, 2.75]
Weng 2008-B	53/118	(44.9%)	27/101	(26.7%)	16.9%	1.68 [1.15, 2.46]
Subgroup Estimate	208/657	(31.7%)	101/611	(16.5%)	I^2: 0%	1.8 [1.49, 2.19]
Follow-up: >12 months						
Punthakee 2024	5/79	(6.3%)	3/80	(3.8%)	1.2%	1.69 [0.42, 6.83]
McInnes 2023	5/79	(6.3%)	5/81	(6.2%)	1.7%	1.03 [0.31, 3.41]
McInnes 2022	6/50	(12.0%)	3/52	(5.8%)	1.4%	2.08 [0.55, 7.87]
McInnes 2020	4/77	(5.2%)	2/77	(2.6%)	0.9%	2.0 [0.38, 10.6]
Hirukawa 2018-A	4/80	(5.0%)	1/58	(1.7%)	0.5%	2.9 [0.33, 25.28]
Hirukawa 2018-B	4/78	(5.1%)	1/58	(1.7%)	0.5%	2.97 [0.34, 25.92]
Shi 2017	37/66	(56.1%)	22/63	(34.9%)	15.3%	1.61 [1.08, 2.39]
Subgroup Estimate	65/509	(12.8%)	37/469	(7.9%)	I^2: 0%	1.64 [1.17, 2.3]
Pooled Estimate					I^2: 0%	1.75 [1.49, 2.04]

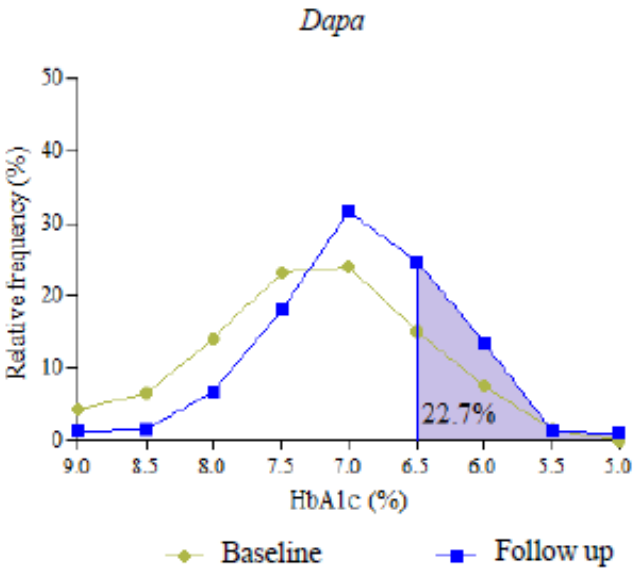
Mantel-Haenszel, DerSimonian-Laird Random Effects Subgroup Effect

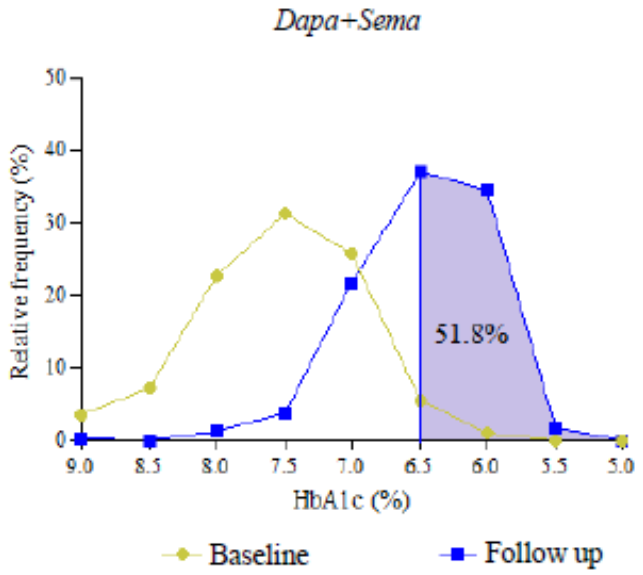


RR: 1,75 (1,49-2,04)

Sherifali DT et al Diabetes Care. 2025 Dec 1;48(12):2181-2191.

Pharmacological remission with dapagliflozin and oral semaglutide





- Multi-center real world study
- 1335 patients enrolled
- 443 Dapa vs 892 Dapa + Sema
- More than 2 fold times percentages of pharmacological remission with combination therapy

Lunati ME et al Pharmacol Res. 2024 Jan;199:107040

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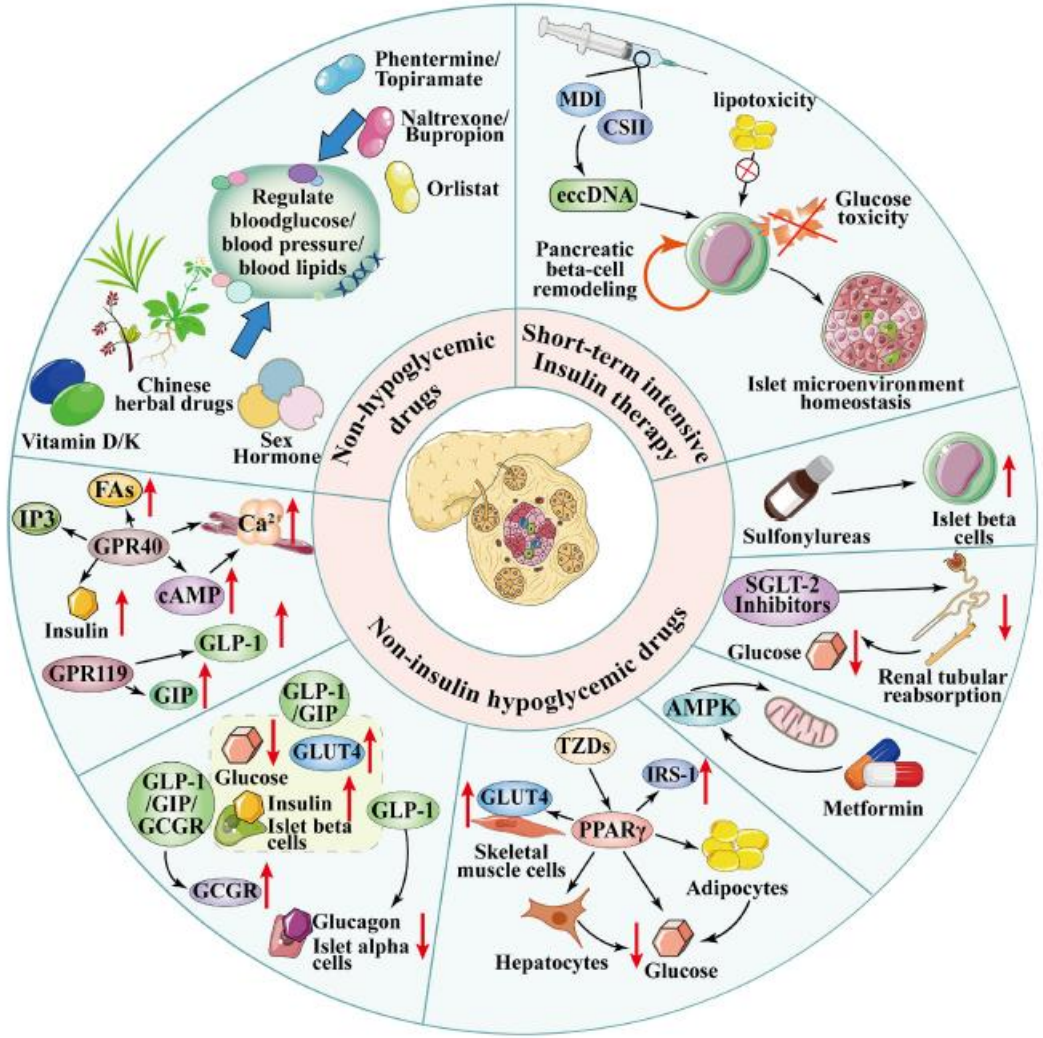
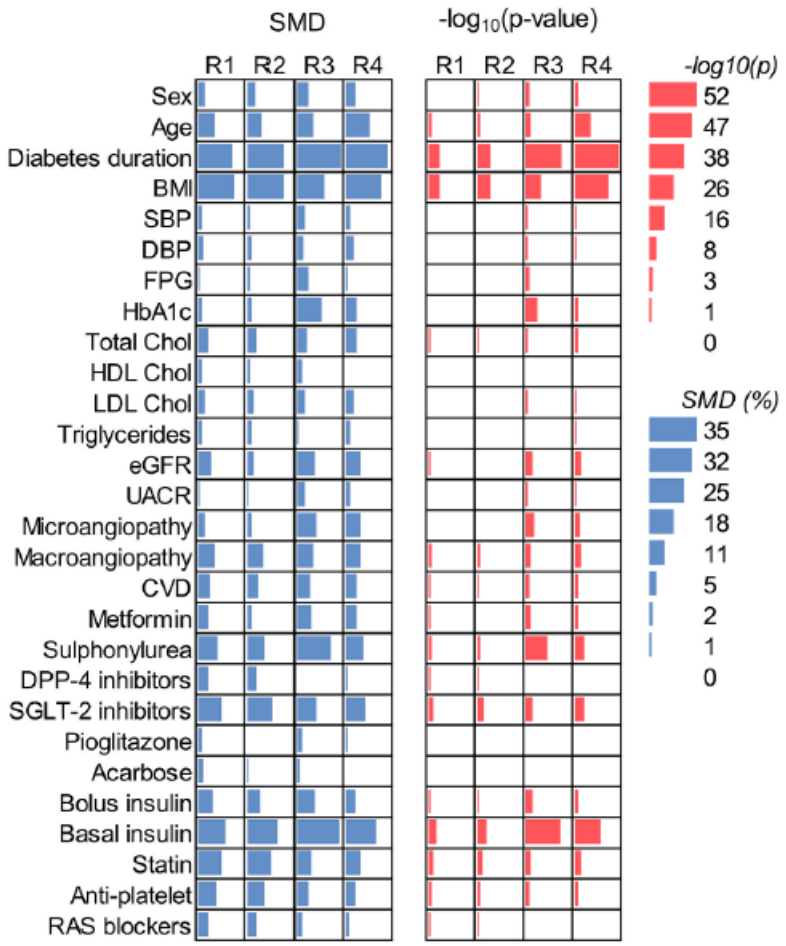
How to target pharmacological remission



Liu Y et al Front Endocrinol (Lausanne). 2025 Dec 5;16:1687601.

Who to target for pharmacological remission?



- ↓ Age
- ↓ Disease duration
- ↑ BMI/ ↑ weight loss
- ↓ burden of complications

Fadini GP at al Lancet Reg Health Eur. 2025 Oct 15;59:101499.

Gregg EW et al JAMA. 2012;308(23):2489–2496.

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L'Evoluzione del Diabete di Tipo 2: Dal Controllo alla Remissione

Traccia l'evoluzione clinica della gestione del diabete di tipo 2, mostrando il passaggio da una visione di malattia cronica alla ricerca della remissione e normoglicemia grazie a studi e nuovi farmaci.

PASSATO: PARADIGMA DEL CONTROLLO (STATICO/PROGRESSIVO)

OGGI: VERSO LA REMISSIONE (DINAMICO/REVERSIBILE)

Pre-2009
Il Paradigma del Controllo

Diabete visto come malattia progressiva e irreversibile; obiettivo HbA1c < 7.0% per prevenire complicanze.

2009
Prime Definizioni ADA

L'ADA introduce la remissione (parziale, completa, prolungata) definita come assenza di farmaci per ≥1 anno.

2014-2018
Studio DiRECT

Dimostrata la remissione (46% a un anno) tramite calo ponderale intensivo gestito in medicina generale.

2021
Consenso Internazionale

Definizione semplificata: HbA1c < 6.5% per almeno 3 mesi senza terapia farmacologica.

OGGI
L'Era dei Nuovi Farmaci

Uso di GLP-1RA, SGLT2i e Tirzepatide per raggiungere la "remissione farmacologica".

Verso la Normoglicemia: Il target si sposta verso HbA1c < 5.7%, un tempo ritenuto irraggiungibile in sicurezza.

Protezione Cardiorenale Integrata: Le nuove terapie offrono benefici indipendenti dal glucosio per cuore e reni.

NORMOGLICEMIA
(HbA1c < 5.7%)
Fino al 51.7%
dei pazienti

REMISSIONE FARMACOLOGICA
(HbA1c < 6.5% con farmaci)
> 50% con terapia combinata

CALO PONDERALE
(Riduzione peso a 52-104 settimane)
Media ~9.5 kg

Conclusions

- Definition of diabetes remission is still matter of debate
- To achieve better remission rate we should act early
- Data regarding long term effects of remission are still lacking
- With new glucose-lowering agents pharmacological remission of diabetes is now possible