Perché e quando serve l'insulina nel trattamento contemporaneo del diabete di tipo 2

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Disclosure

- Concetta Irace dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Abbott
- Lilly Boehringer
- Medtronic
- Novo Nordisk
- Roche Diabetes Care Italia
- Theras
- Sanofi

- *Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, etc.)*

The modern role of BI in advancing therapy in people with T2D

Table 2—Clinical scenarios in which starting BI may be preferred or not preferred in the era of the innovative medications, GLP-1RA and SGLT2i

Preferred
Metabolic emergencies (hyperosmolality, ketoacidosis)
Acute or variable hyperglycemia (sick days, steroid therapy, trauma, major surgery, stress)
Patient preference
Comorbidities (kidney and liver failure, cancer, chemotherapy)
Autoimmune pathogenesis (LADA)
Pregnancy
Lean, predominantly insulin-deficient T2DM
• including some elderly onset
• with excessive weight loss on other therapies
New-onset T2DM with marked hyperglycemia
HbA_{1c} not at target with other management
Intolerance of noninsulin therapies (including GLP-1RA, SGLT2i)
Possibility that patient may have T1DM
Not preferred
Specific indication for other medication (HF, CKD risk, acute CV protection)
Obesity
Nonpreference by the potential user*

HF, heart failure. *Nonpreferred as first choice, but BI may be added on later to other therapies to lower HbA_{1c}.

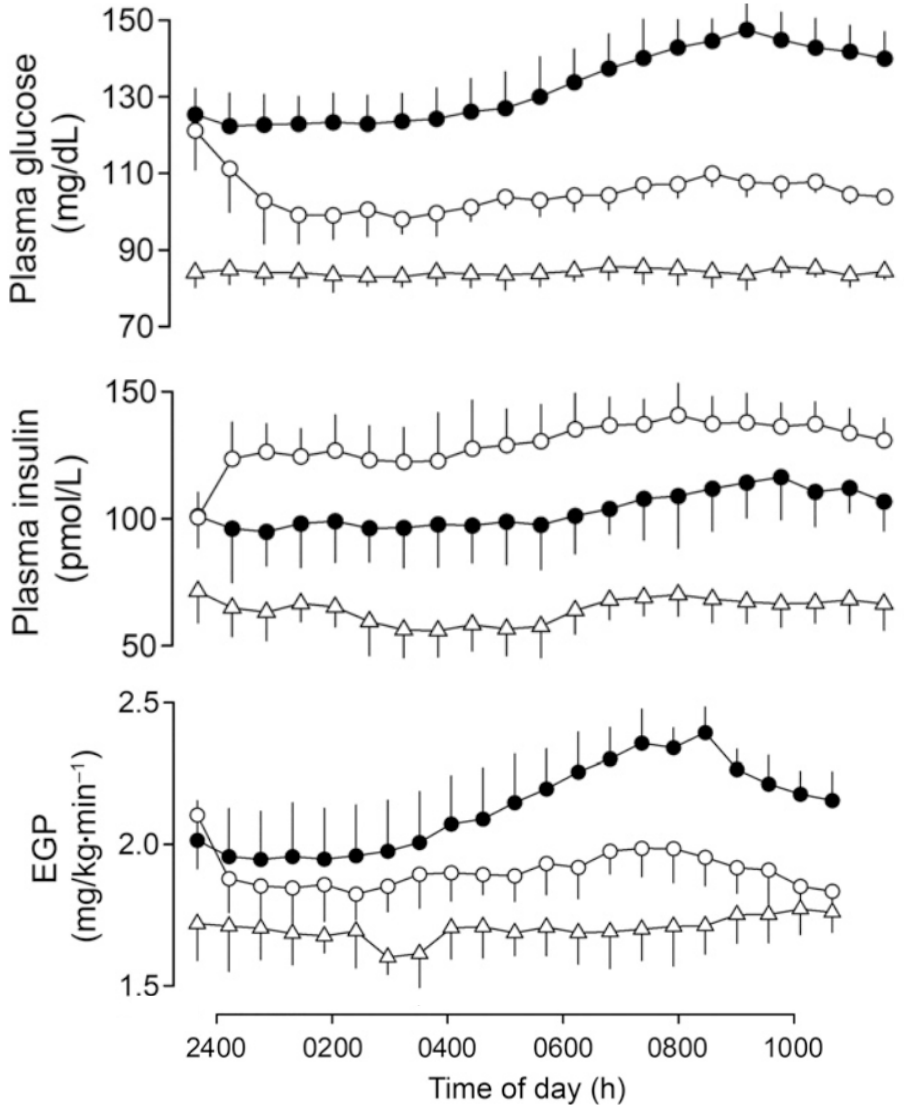
Diabetes Care 2025;48:671-681

Early basal insulin deficiency in type 2 diabetes

△ 8 individuals **without diabetes**

● 11 untreated individuals with recently diagnosed **T2DM** studied once with **saline** infusion.

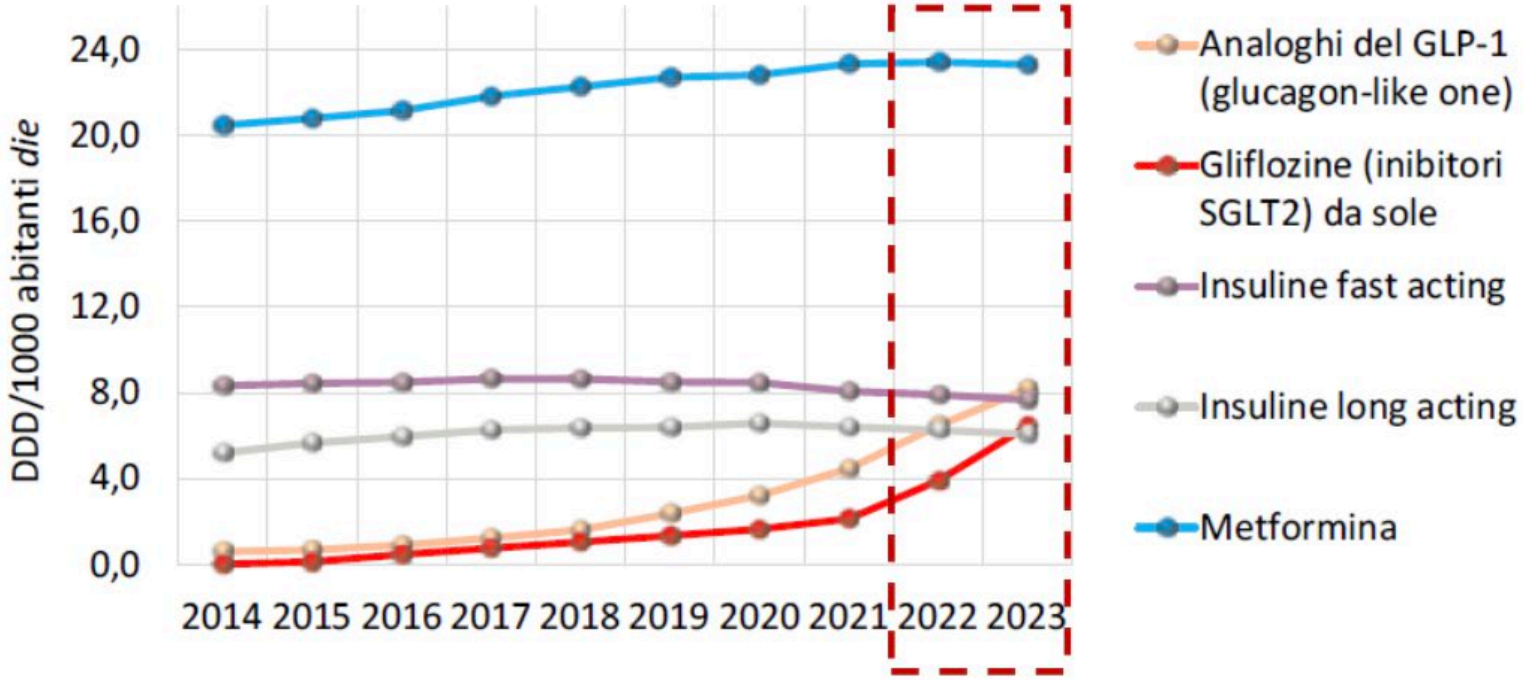
○ 11 untreated individuals with recently diagnosed **T2DM** with feedback intravenous **insulin** infusion.



Williams Textbook of Endocrinology. 14th ed. Philadelphia, PA, Elsevier, 2020, p. 1338–1348.e3
Diabetes 2023;72:1364–1373

Analisi dati di consumo farmaci da report OSMED – AIFA (2023-2024)

Figura 3.3.1a Antidiabetici, andamento temporale 2014-2023 del consumo (DDD/1000 abitanti *die*) dei sottogruppi a maggior spesa



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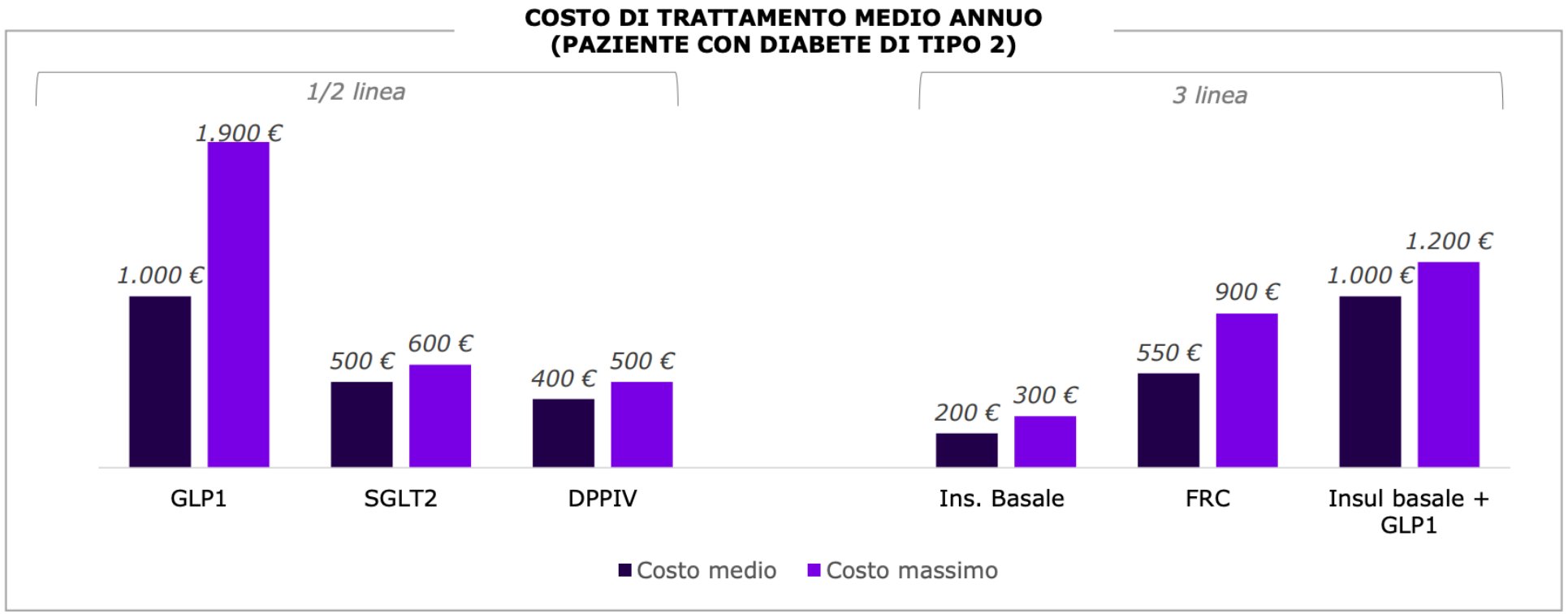
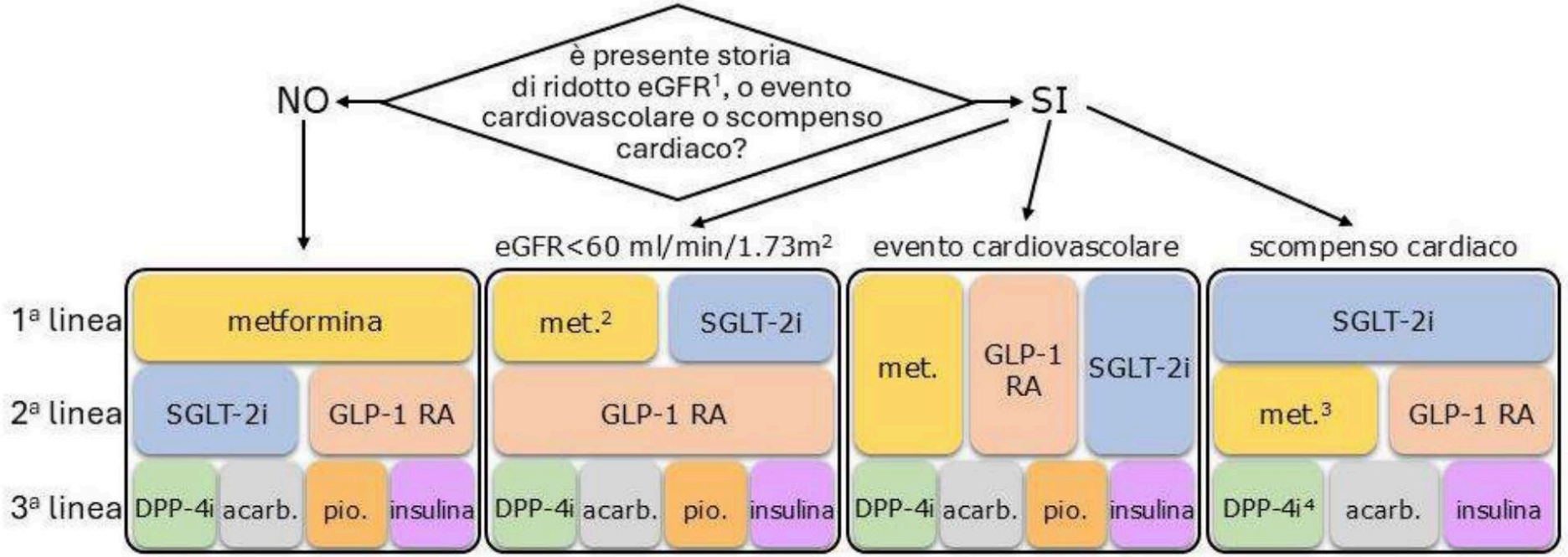


Linea Guida della Società Italiana di Diabetologia (SID) e dell'Associazione dei Medici Diabetologi (AMD)



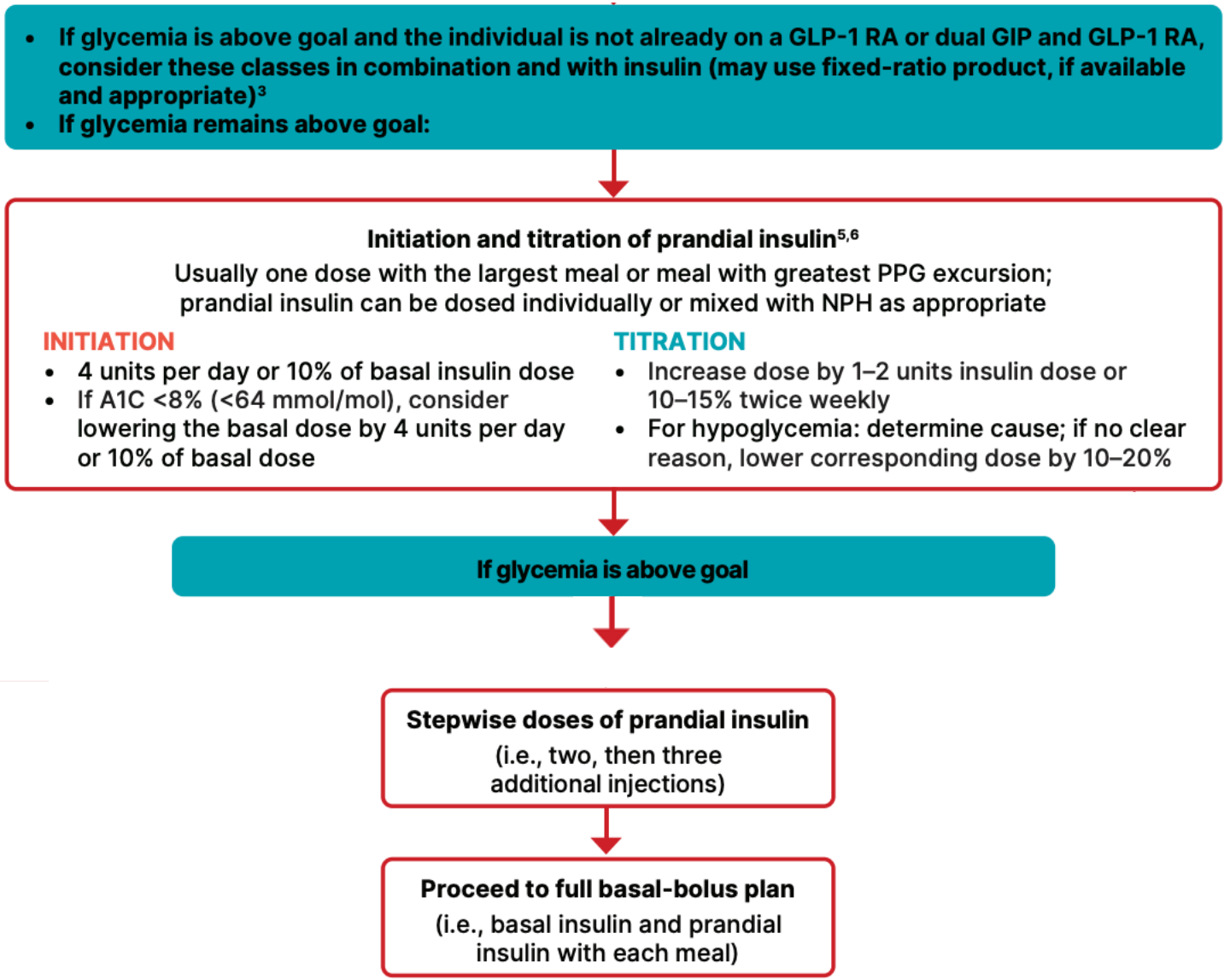
NB: l'indicazione ai farmaci di terza linea (DPP-4i, acarbosio, pioglitazone, insulina) deve essere considerata solo dopo l'utilizzo in combinazione di metformina, SGLT-2i e GLP-1 RA, qualora tollerati e non controindicati. L'indicazione per DPP-4i è valida solo se GLP-1 RA non indicati o non tollerati. 1. si intende eGFR secondo CKD-EPI < 60 ml/min/1.73m²; 2. se la metformina non è controindicata per eGFR<30 ml/min/1.73m²; 3. se la metformina non è controindicata per ridotta funzione cardiaca; 4. eccetto saxagliptin che non è indicato in caso di scompenso cardiaco.
Si raccomanda la deprescrizione di sulfoniluree e repaglinide.

Guidance on starting and titrating of BI in people with T2D

Insulin dosing	
Initial BI dose	0.1 or 0.2 units/kg/day (depending on high or low insulin sensitivity, respectively)
Target FPG	100–120 mg/dL (5.6–6.6 mmol/L) in absence of hypoglycemia
Algorithm of titration	Titration 1–2 times/week*
	Measure FPG every morning and consider the values from at least three consecutive days at 2–5 days after last dose change
	Consider the median (the middle number) FPG value of the three consecutive days, as well as any unexplained low results (<80 mg/dL)
	• >120 mg/dL and none <80 mg/dL: increase dose by 2 units/day
	• 100–120 mg/dL: no dose change
	• <100 mg/dL or any <80 mg/dL: decrease dose by 2 units/day
Cessation of titration	If median FPG is to target (continue BI)
	If median FPG is above target and where there is unexplained confirmed (including biochemical) hypoglycemia (consider prandial insulin dosing)
	If median FPG is approaching target (<140 mg/dL) but postprandial excursions (>100 mg/dL) suggest that most glucotoxicity is meal related (consider prandial insulin dosing[s])
Longer-term titration	Expect continued increase in basal dose over months/years
	Expect need for mealtime insulin (FPG to target, but HbA_{1c} not, and/or prandial glucose excursions >100 mg/dL)
Clinic monitoring	
Virtual contact	Every few days/weeks during active titration
Monitoring of HbA_{1c}	Every 3 months
Clinic visit in person	Every 3–4 months or as required

FPG was self-measured. §This is only one of the several validated ways to titrate BI. *Can be done by the patient after appropriate education (69,70).

Diabetes Care 2025;48:671-681


If glycemia is above goal and the individual is not already on a GLP-1 RA or dual GIP and GLP-1 RA, consider these classes in combination and with insulin (may use fixed-ratio product, if available and appropriate)[3]
If glycemia remains above goal:
Initiation and titration of prandial insulin[5,6]
Usually one dose with the largest meal or meal with greatest PPG excursion; prandial insulin can be dosed individually or mixed with NPH as appropriate
INITIATION
4 units per day or 10% of basal insulin dose
If A1C <8% (<64 mmol/mol), consider lowering the basal dose by 4 units per day or 10% of basal dose
TITRATION
Increase dose by 1–2 units insulin dose or 10–15% twice weekly
For hypoglycemia: determine cause; if no clear reason, lower corresponding dose by 10–20%
If glycemia is above goal
Stepwise doses of prandial insulin
(i.e., two, then three additional injections)
Proceed to full basal-bolus plan
(i.e., basal insulin and prandial insulin with each meal)

Combination of BI with other therapies

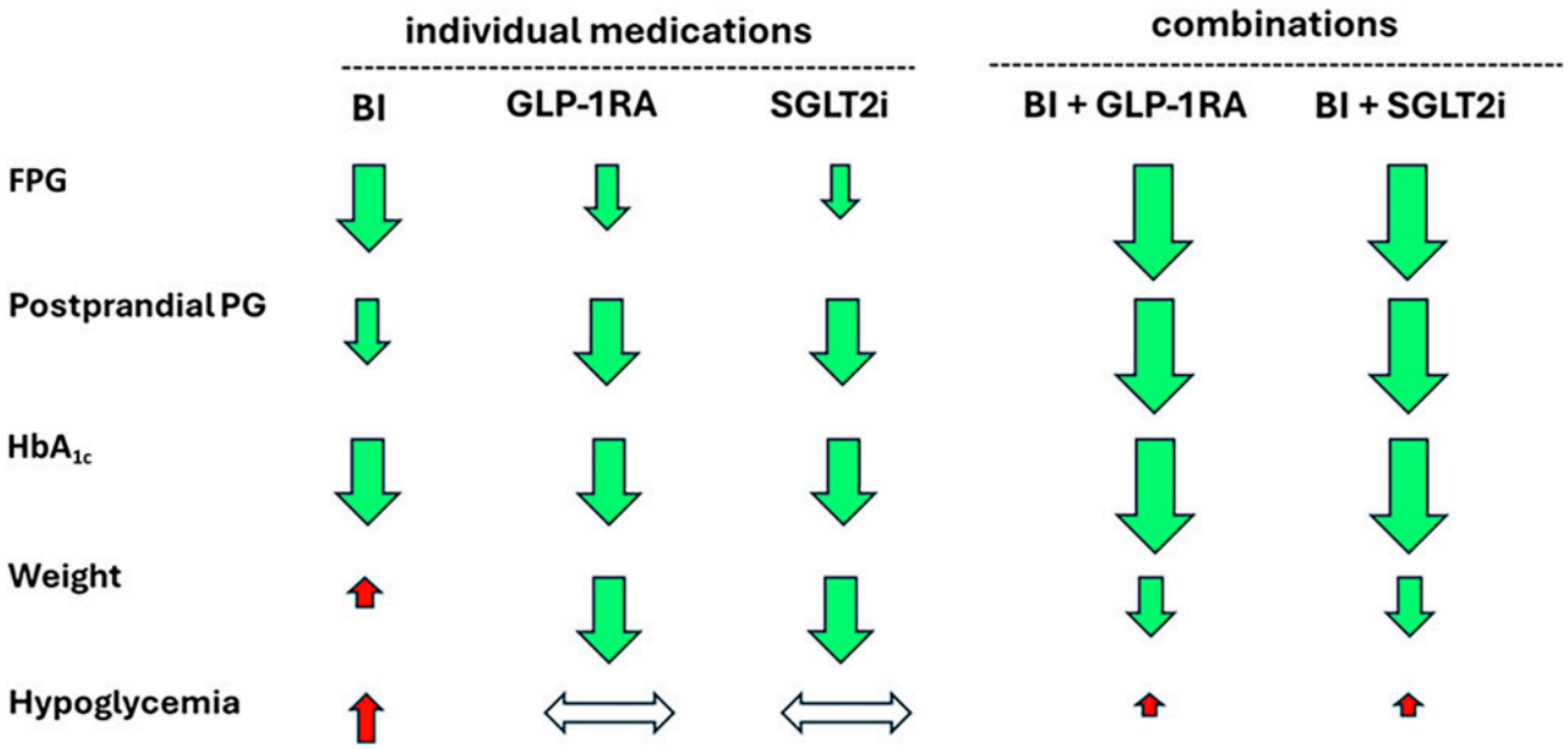
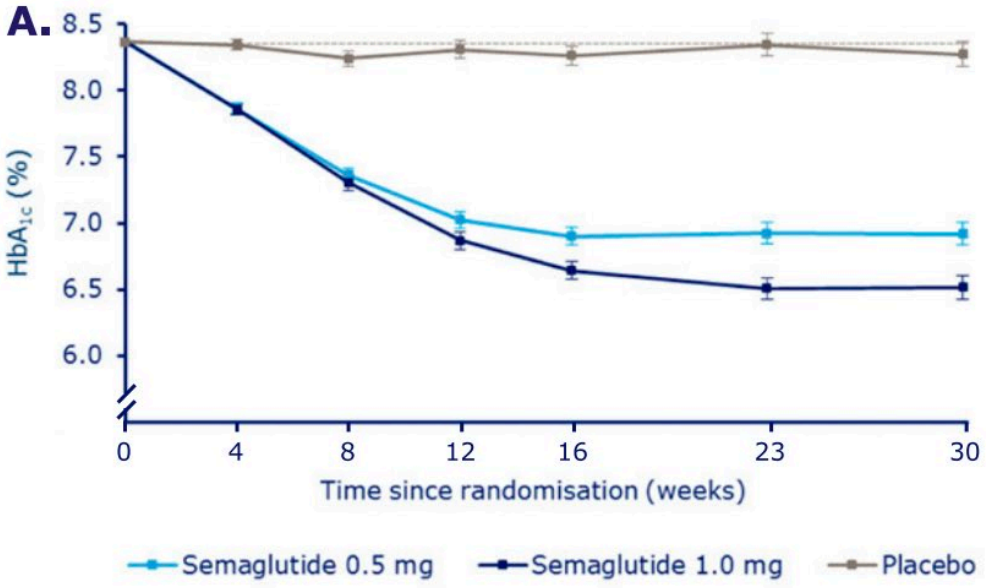
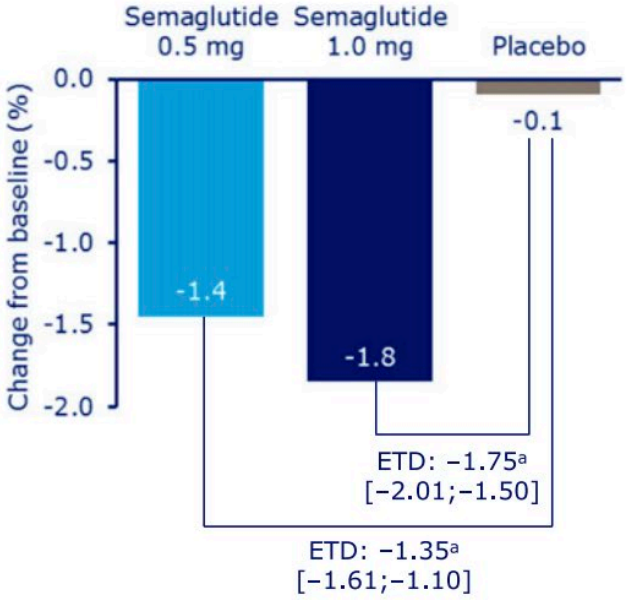


Figure 3—Metabolic outcomes of individual and combined treatments with BI, GLP-1RA, and SGLT2i. Cardiorenal-protective effects of GLP-1RA and SGLT2i are not represented here. Long-term protective effects of HbA_{1c} at target through BI on macroangiopathy also are not represented.

Combination of BI with GLP-1 RA

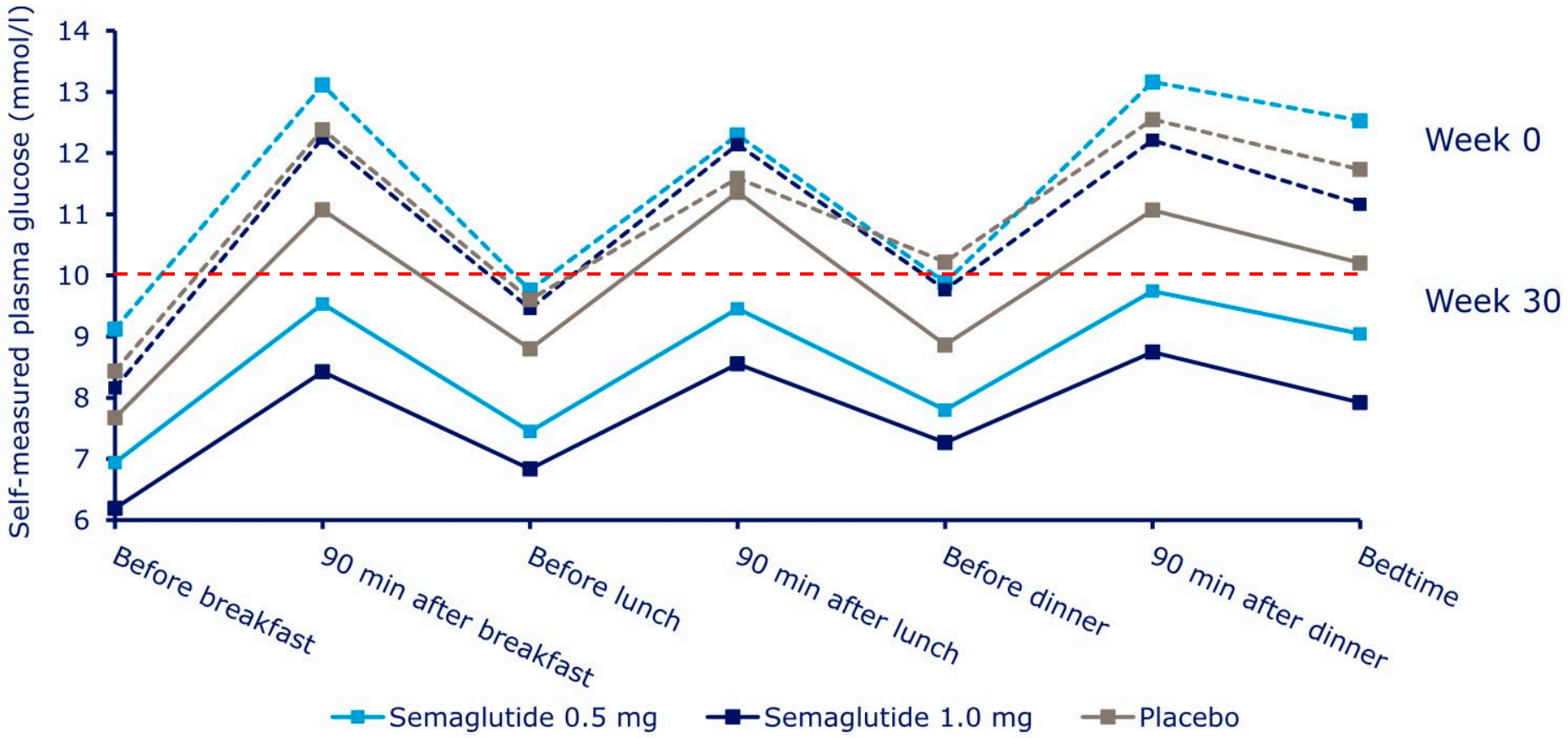
- **GLP-1RA** should be added to BI treatment when postprandial **PG** and **HbA1c** increase above the target despite well-controlled FPG with BI.
- **BI** should be added to a preexisting treatment with GLP-1RA whenever **FPG** and **HbA1c** do not decrease to target, or when the target is no longer maintained.





Sustain 5 J Clin Endocrinol Metab, 2018, 103(6):2291–2301

Mean seven-point self-measured blood glucose profile at baseline and at week 30



Sustain 5 J Clin Endocrinol Metab, 2018, 103(6):2291–2301

Hypoglycemic events

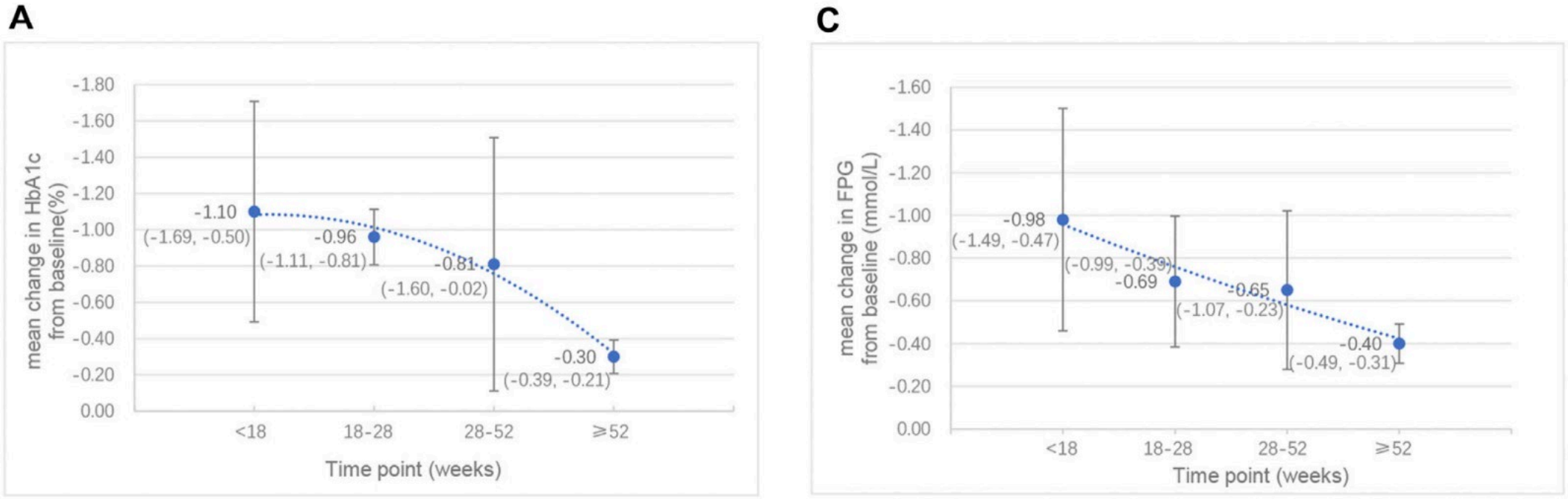
	Semaglutide 0.5 mg				Semaglutide 1.0 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
N	132				131				133			
Severe or blood glucose-confirmed symptomatic[a]	11	(8.3)	17	20.2	14	(10.7)	25	30.5	7	(5.3)	13	15.5
Nocturnal severe or blood glucose-confirmed symptomatic[a]	2	(1.5)	3	3.6	4	(3.1)	6	7.3	4	(3.0)	6	7.1
Severe	0				2	(1.5)	2		1	(0.8)	1	
Nocturnal severe	0				0				0			
In subjects with HbA_{1c} ≤8% at screening												
N	49				49				49			
Severe or blood glucose-confirmed symptomatic	4	(8.2)	5	15.7	8	(16.3)	14	46.5	2	(4.1)	3	9.9
In subjects with HbA_{1c} >8%												
N	83				82				84			
Severe or blood glucose-confirmed symptomatic	7	(8.4)	12	22.9	6	(7.3)	11	21.2	5	(6.0)	10	18.6

Severe or blood-glucose-confirmed symptomatic hypoglycemia: an episode that is severe according to the ADA classification or blood glucose-confirmed by a plasma glucose value below 3.1 mmol/l (56 mg/dl) with symptoms consistent with hypoglycemia.

[a]The estimated odds for experiencing severe or blood glucose-confirmed episodes did not differ statistically significantly with both doses of semaglutide when compared with placebo. E, number of events; HbA_{1c}, glycated hemoglobin; N, number of subjects; R, events per 100 patient years of exposure.

Sustain 5 J Clin Endocrinol Metab, 2018, 103(6):2291–2301

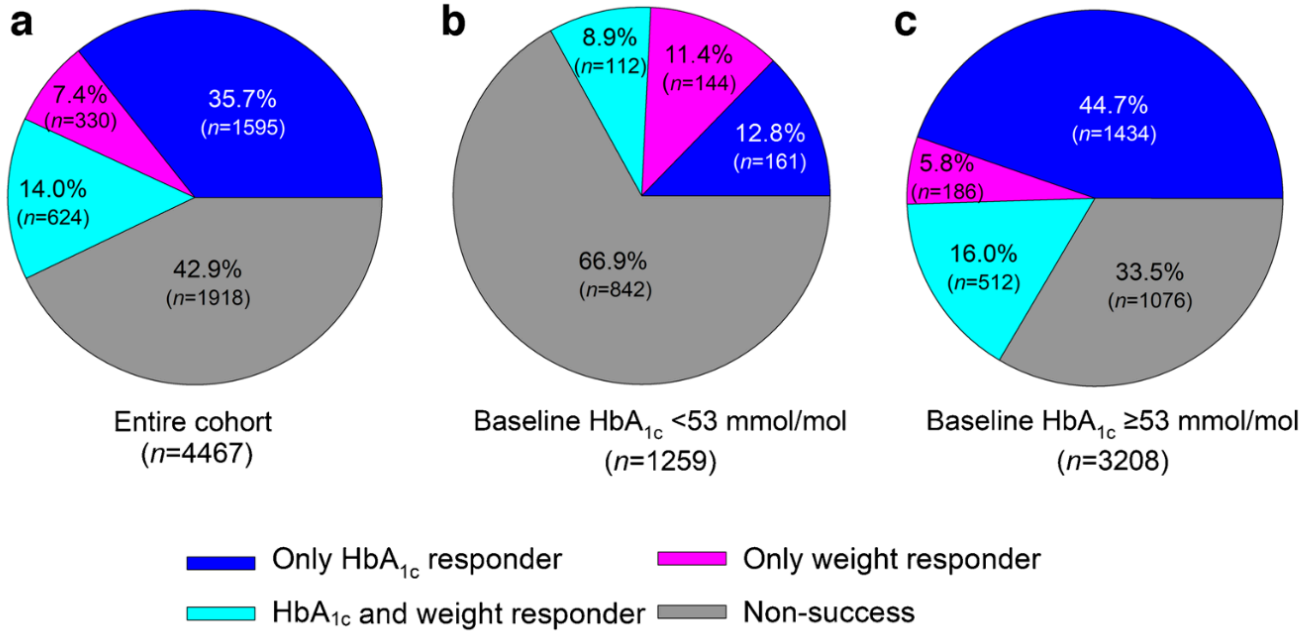
The Efficacy and Safety of the Combination Therapy With GLP-1 Receptor Agonists and SGLT-2 Inhibitors in Type 2 Diabetes Mellitus: A Systematic Review and Meta-analysis

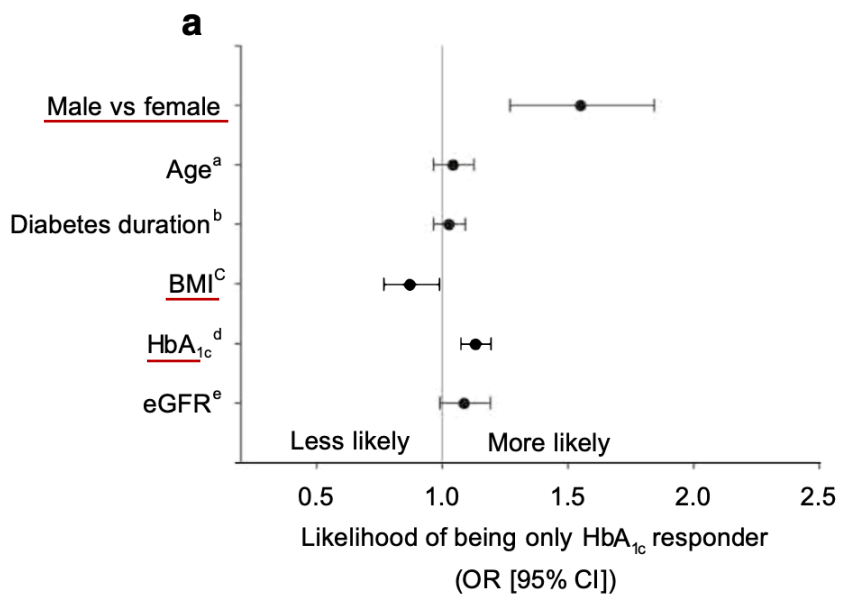


Line chart of the mean changes in (A) HbA1c (%), (C) FPG (mmol/L) between the combination therapy of GLP-1RA and SGLT-2i and their monotherapy by week. *Data are presented as mean (95% CI).

Frontiers in Pharmacology doi.org/10.3389/fphar.2022.838277

Heterogeneity in response to GLP-1 receptor agonists in type 2 diabetes in real-world clinical practice: insights from the DPV register – an IMI-SOPHIA study

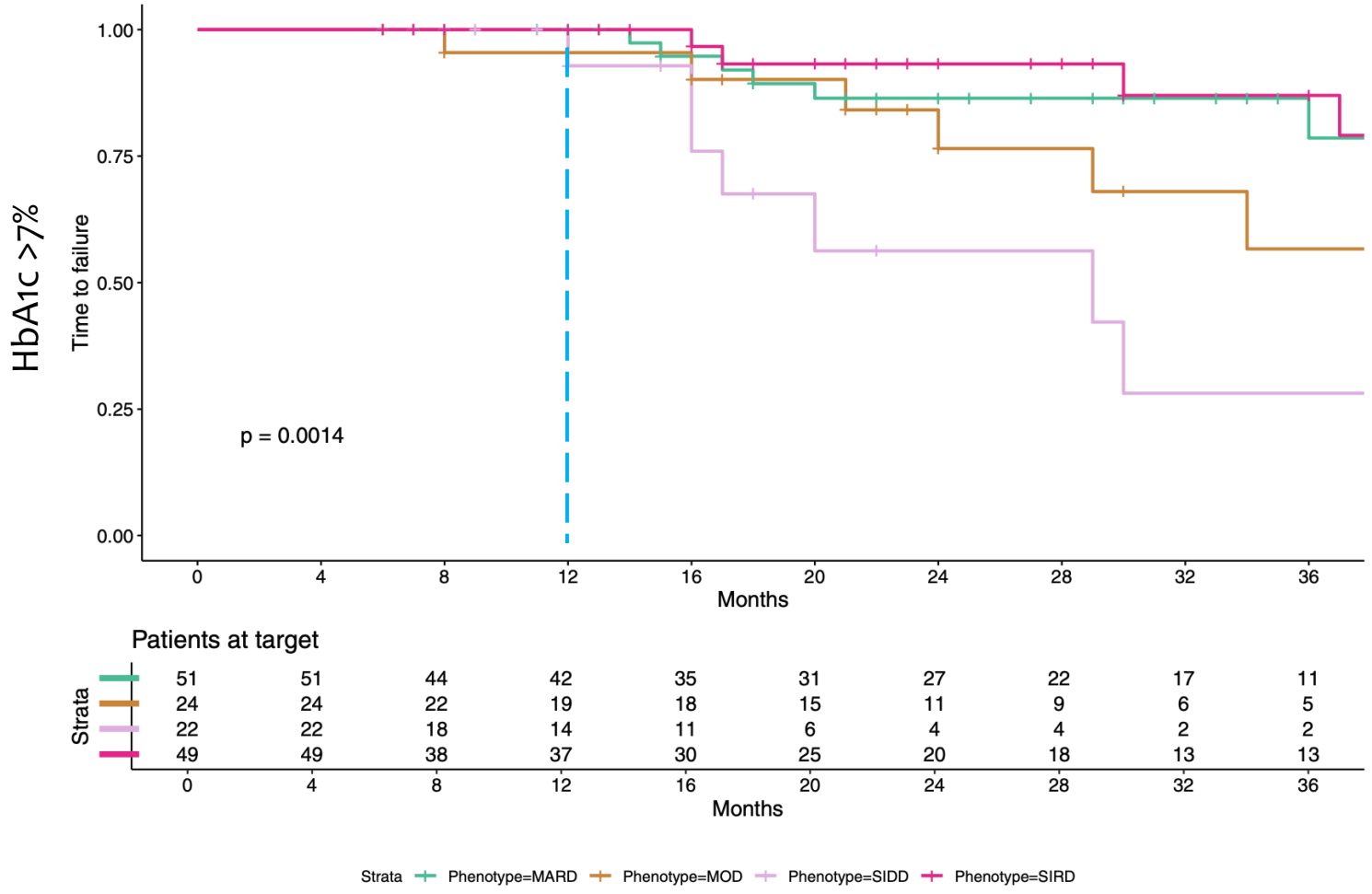




- Cohort **4467**
- Follow-up **6 months**
- HbA1c responders ↓ **≥0.5%**
- Body Weight responders ↓ **≥5%**

Diabetologia; 2025 68:1666–1673

Effectiveness of GLP-1RA according to different type 2 diabetes phenotypes: A retrospective study



- **MARD**, mild age-related diabetes;
- **MOD**, mild obesity-related diabetes;
- **SIDD**, severe insulin-deficient diabetes;
- **SIRD**, severe insulin-resistant diabetes.

Diabetes Obes Metab. 2025;27:6210–6219

Conclusioni

- Nel diabete di tipo 2 il **deficit** della secrezione insulinica è presente già all'esordio e peggiora con il tempo;
- L'introduzione della insulina basale è una appropriata strategia per il **meccanismo patogenetico;**
- Nelle persone con diabete in trattamento con **farmaci innovativi,** l'introduzione della insulina basale è spesso necessaria per raggiungere gli obiettivi glicemici e contenere eventuali effetti collaterali delle altre terapie;
- I **meccanismi di azione complementari** tra insulina basale e terapia innovativa devono incoraggiare la terapia combinata;
- L'insulina basale è una strategia nel fenotipo con **deficit insulinico;**
- La combinazione di insulina basale ed insulina ad azione rapida (**basal plus e basal bolus**) interessa meno del 5% delle persone con diabete coinvolte negli studi registrativi ed è una strategia da valutare il base alla storia clinica e anamnesi farmacologica delle persone con diabete.