Riduzione del rischio cardiovascolare nel diabete tipo 2: approccio stepwise o precoce e più intensivo? I target metabolici orientano la strategia

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UNIVERSITÀ DEGLI STUDI DELL'AQUILA

MESVA

Conflitto di Interessi

Negli ultimi due anni Marco G. Baroni ha ricevuto compensi per relazioni e/o consulenze da:

- Lilly, Novo Nordisk, Boheringer, Abbot, Pikdare, Viatris

La struttura di apparteneza di MG Baroni ha ricevuto:

- Compensi per studi clinici sponsorizzati da: Novo Nordisk

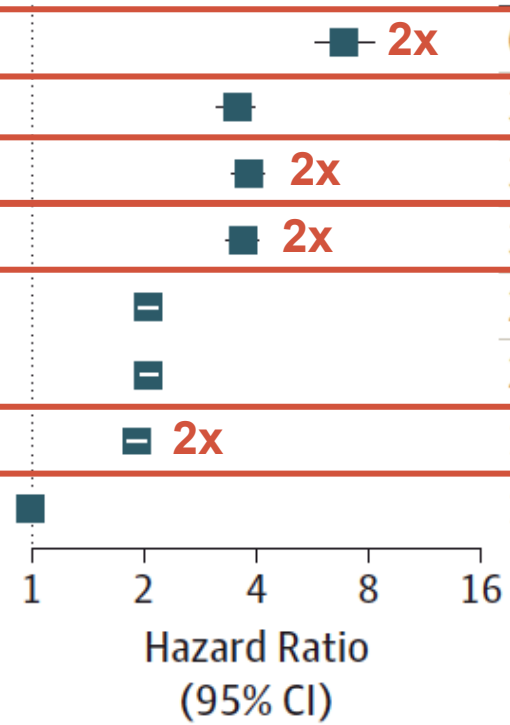
Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi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

AGENDA

- Il carico della Malattia Cardiovascolare (CVD)
- La «memoria metabolica»
- Complessità patogenetica del diabete
- Terapia di combinazione precoce vs stepwise

Association of Cardiometabolic Multimorbidity With Mortality

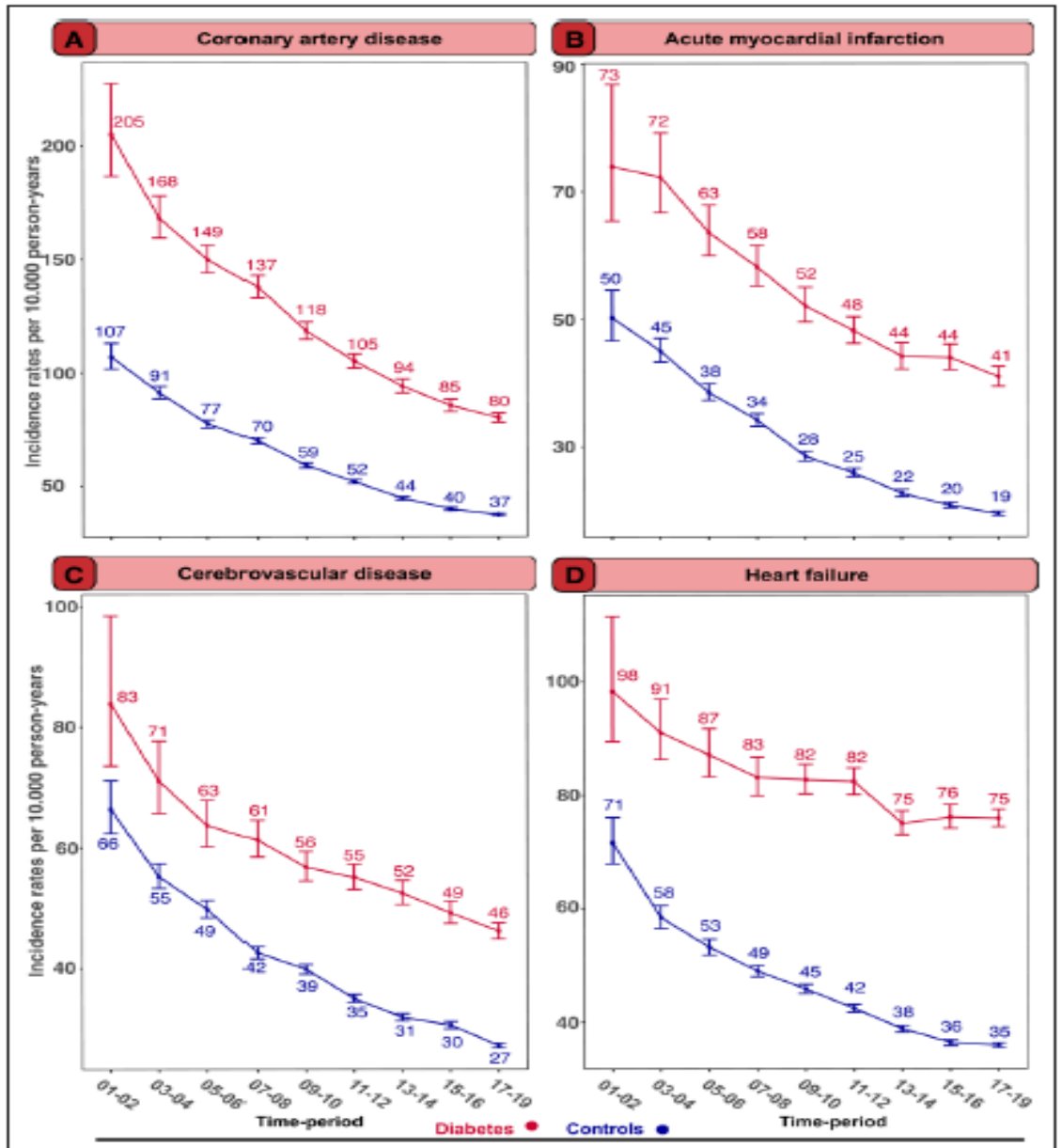
Disease Status at Baseline	No of. Participants	No. of Deaths	Person-Years	Hazard Ratio (95% CI)	I^2 (95% CI)
Diabetes, stroke, and MI	541	379	3584	6.9 (5.7-8.3)	51 (38-62)
Stroke and MI	1836	1174	14210	3.5 (3.1-4.0)	61 (52-69)
Diabetes and stroke	1321	778	10234	3.8 (3.5-4.2)	18 (0-38)
Diabetes and MI	3233	1794	25321	3.7 (3.3-4.1)	69 (62-75)
MI	21591	9636	216081	2.0 (1.9-2.2)	84 (80-86)
Stroke	8583	3814	82208	2.1 (2.0-2.2)	50 (36-61)
Diabetes	24677	8087	254608	1.9 (1.8-2.0)	76 (70-80)
None	627518	103181	8772977	1 [Reference]	



The Emerging Risk Factors Collaboration ***JAMA***. 2015;314:52-60.

Standardized incidence rates for all cardiovascular outcomes among individuals with type 2 diabetes and matched control subjects. 20 years follow-up

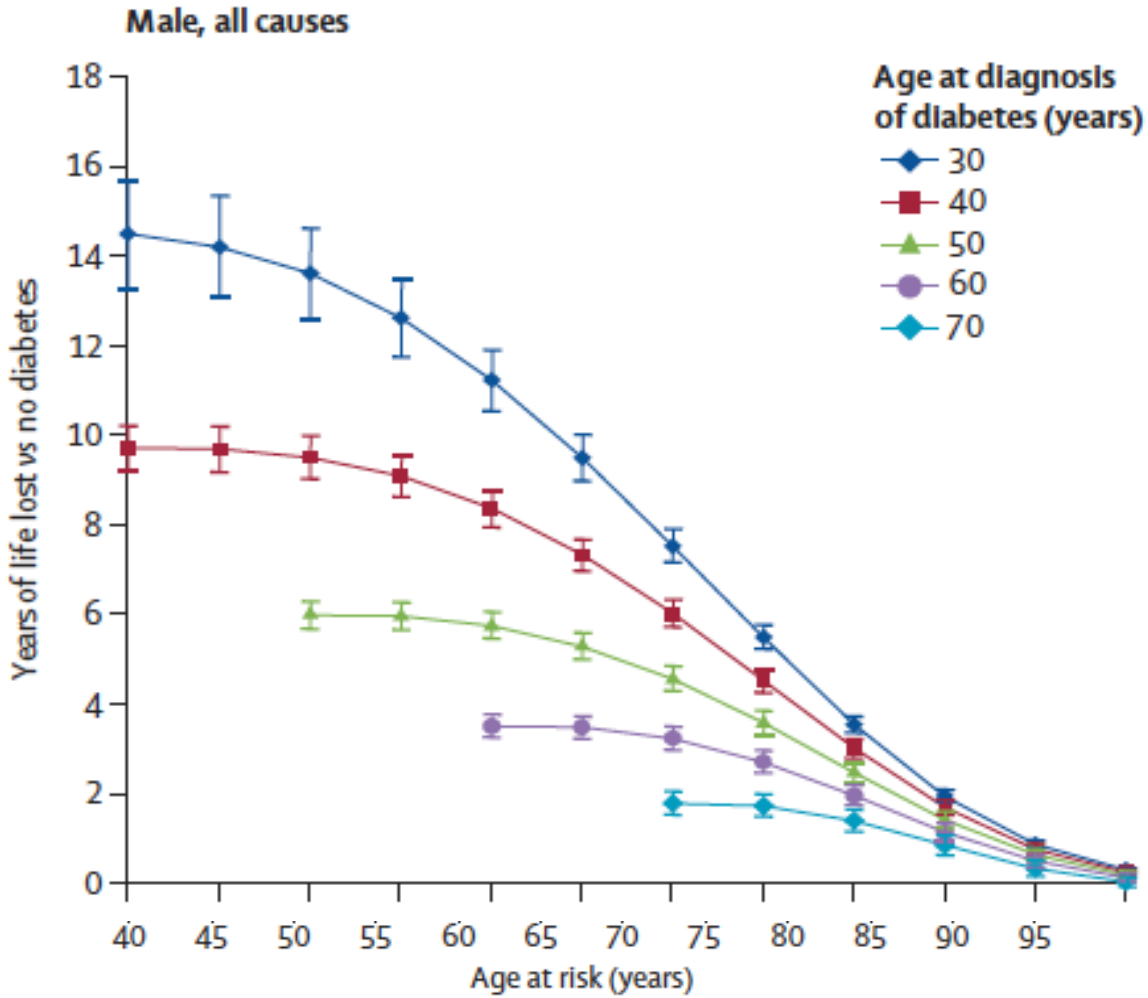
- 679 072 individuals with T2D from the Swedish National Diabetes Register
- 2 643 800 matched control subjects

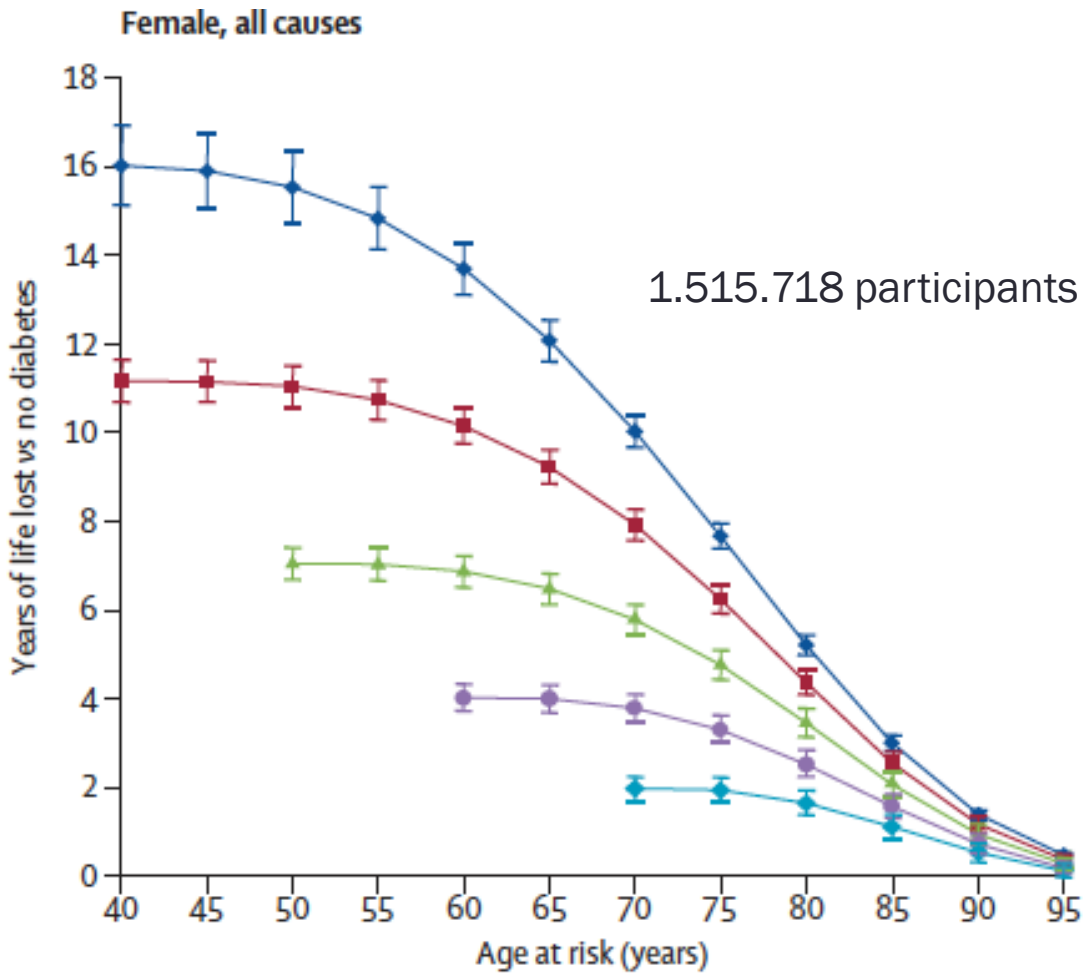


Sattar N et al. Circulation. 2023

Estimated years of life lost by age at diagnosis of type 2 diabetes compared with people without diabetes

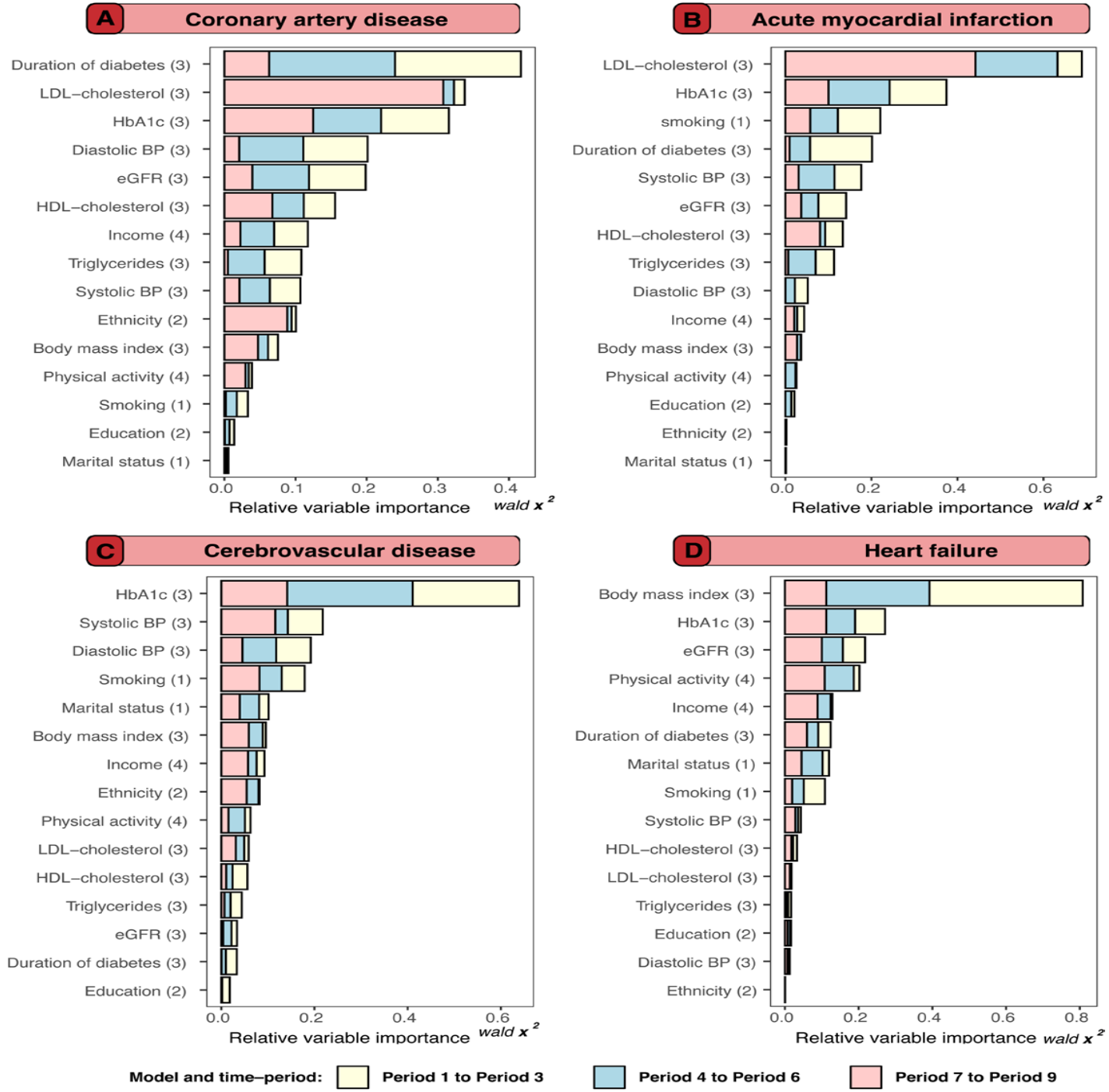
Emerging Risk Factors Collaboration, Lancet 2023





1.515.718 participants

Risk fators importance for cardiovascular outcomes among individuals with type 2 diabetes and matched control subjects.
20 years follow-up



Sattar N et al. Circulation. 2023

History of UKPDS



Trial
1977 to 1997

Monitoring
1997 to 2007

NHS data
2007 to 2021

20 years

10 years

14 years

42,977 person-years

66,972 person-years

78,349 person-years; range 0 to 42 years; 14 participants > 40 years

ukpds

Impact of Intensive Glucose Control with Sulfonylurea/Insulin

		Median Follow-up		
		10.0y	*16.9y*	*17.4y*
Aggregate Endpoint		**1997**	**2007**	**2021**
Any diabetes-related endpoint	*RRR:*	12%	9%	10%
	P:	0.029	0.040	0.016
Myocardial infarction	*RRR:*	16%	15%	15%
	P:	0.052	0.014	0.0074
Microvascular disease	*RRR:*	25%	24%	26%
	P:	0.0099	0.001	<0.0001
All-cause mortality	*RRR:*	6%	13%	11%
	P:	0.44	0.007	0.0093

RRR = Relative Risk Reduction, P = Log Rank

UKPDS 33 Lancet 1998;352:837-853. UKPDS 80. N Engl J Med 2008;359:1577-89. Unpublished data

ukpds

Impact of Intensive Glucose Control with Metformin

		Median Follow-up		
		10.7y	*17.7y*	*18.0y*
Aggregate Endpoint		**1997**	**2007**	**2021**
All-cause mortality	*RRR:*	36%	27%	25%
	P:	0.011	0.002	0.002

Il buon controllo glicemico a partire dalle prime fasi della malattia sembra avere un effetto di riduzione del rischio cardiovascolare a lungo termine (memoria metabolica)

RRR = Relative Risk Reduction, P = Log Rank

UKPDS 33 Lancet 1998;352:837-853. UKPDS 80. N Engl J Med 2008;359:1577-89. Unpublished data ukpds

ACCORD, ADVANCE e VADT: risultati

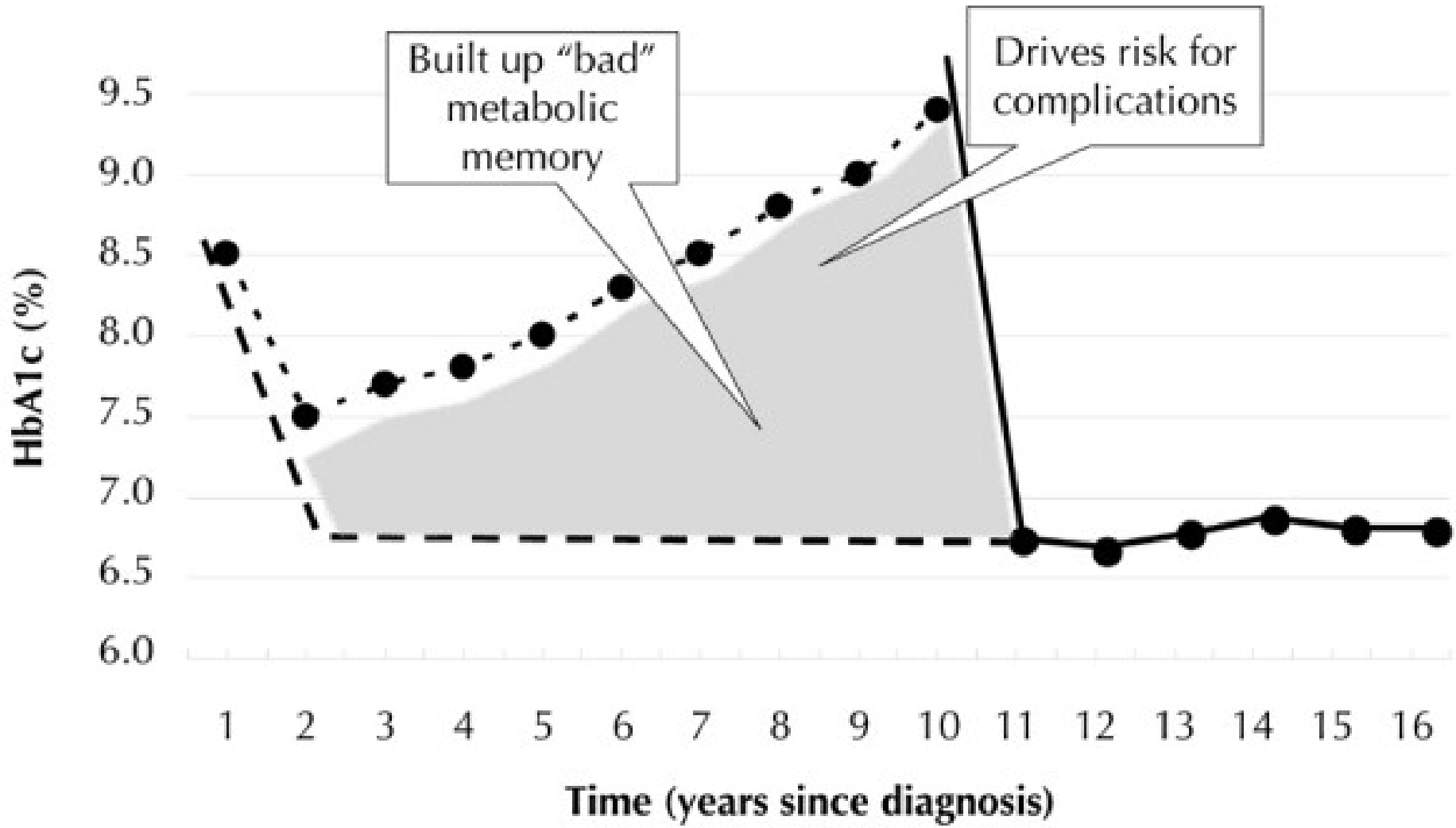
	ACCORD[1]	ADVANCE[2]	VADT[3]
Numeri	10,251	11,140	1,791
Endpoint CVD primario	↓ 10% (p=0.16)	↓ 6% (p=0.37)*	↓ 13% (p=0.12)
Mortalità (complessiva)	↑ 22% (p=0.04)	↓ 7% (p=NS)	↑ 6.5% (p=NS)
Mortalità cardiovascolare	↑ 39% (p=0.02)	↓ 12% (p=NS)	↑ 25% (p=NS)

Macro e micro combinati: ↓10% ↓, p=0.013 *endpoint microvascolare: ↓14% ↓, p=0.015

Durata di diabete: 8-12 anni

1. N Engl J Med 2008;358:2545-59;
2. N Engl J Med 2008;358:2560-72;
3. N Engl J Med 2009;360:129-39;

Hypothetical representation of the natural history of diabetic patients recruited in «Intensive Diabetes Trials»



Simulation of 2 Glycaemic Legacy Effect Scenarios

50-year old male with newly-diagnosed T2D and HbA_{1c} = 8%



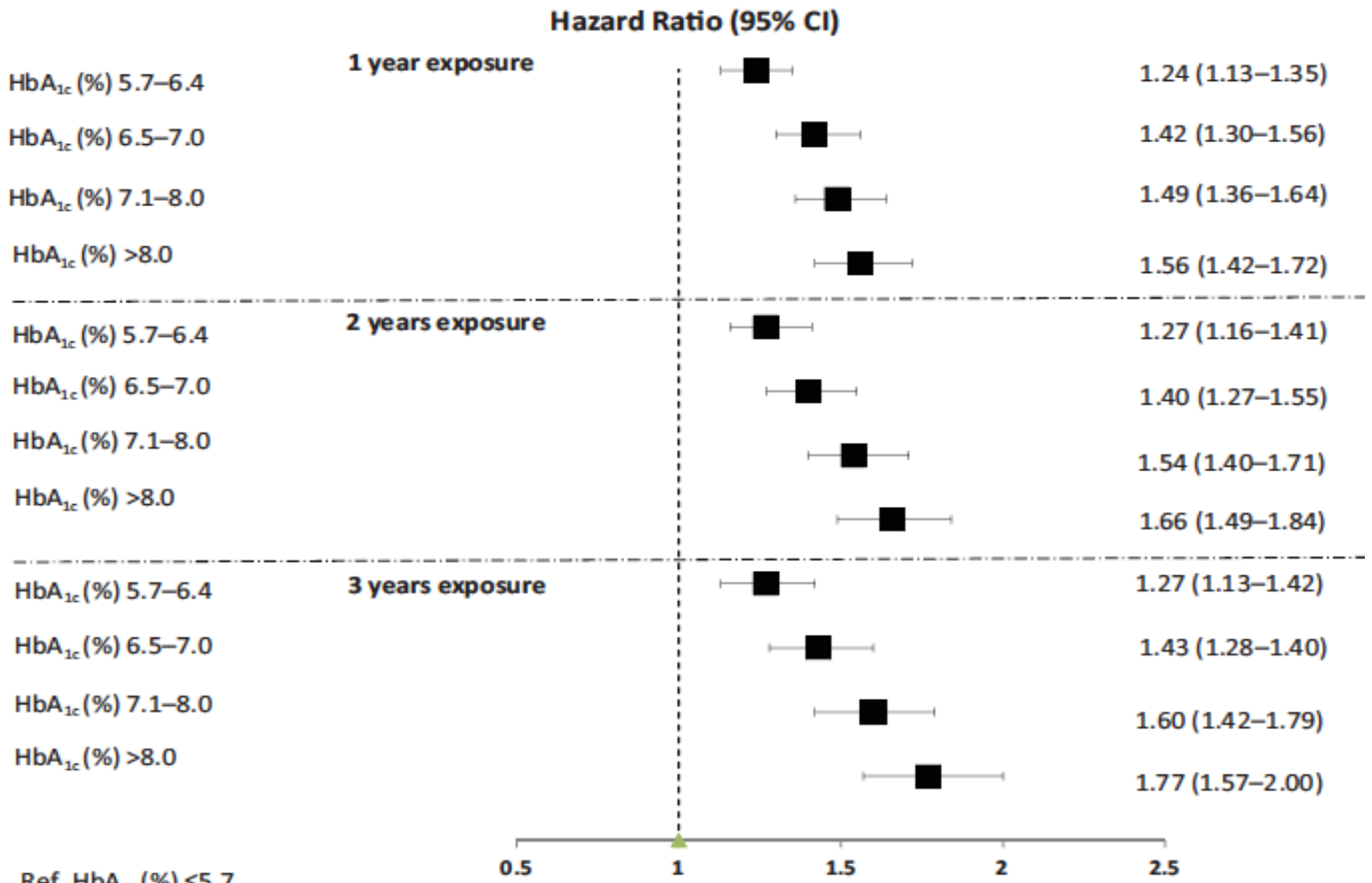
UKPDS 88. Diabetes Care 2021;44:2231-2237.

ukpds

diabetes
American Diabetes Association

When Does Metabolic Memory Start? Insights From the Association of Medical Diabetologists Annals Initiative on Stringent HbA_{1c} Targets

AMD 2025 (N = 251.339)

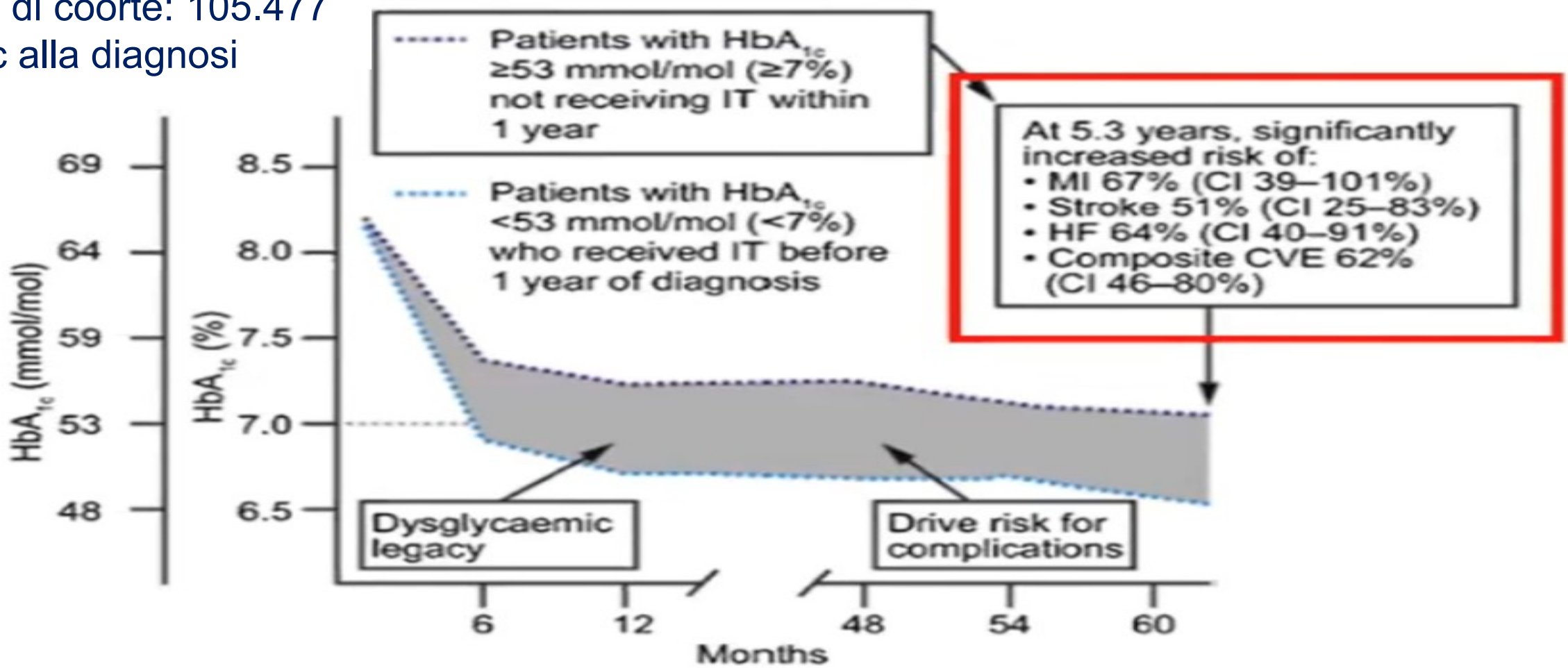


Russo GT et al. Diabetes 2025;74(1):75–81

Delay in treatment intensification increases the risks of cardiovascular events in patients with type 2 diabetes

Sanjoy K Paul[1*†], Kerenaftali Klein[1], Brian L Thorsted[2], Michael L Wolden[2] and Kamlesh Khunti[3†]

Studio di coorte: 105.477
HbA1c alla diagnosi
8,19%



Paul et al. Cardiovasc Diabetol (2015) 14:100

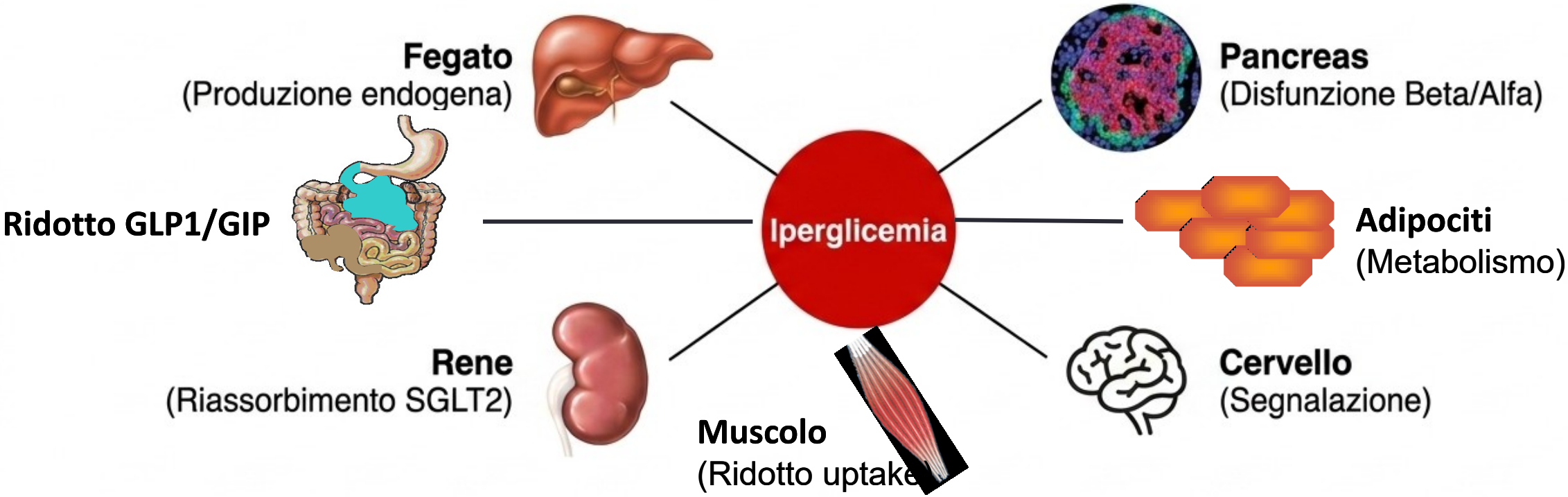
Il nuovo target ambizioso: HbA1c < 5.7%



Storicamente, il rischio di ipoglicemia limitava i target (es. 6.5% - 7.0%).

Il Paradigma Attuale: Le nuove classi farmacologiche (SGLT2-i, GLP1-RA) permettono di raggiungere range glicemici "normali" (<5.7%) azzerando il rischio di ipoglicemie.

La complessità patogenetica del diabete richiede interventi multipli



Il DMT2 è una patologia multifattoriale. Un singolo farmaco (monoterapia) bersaglia solo 1 o 2 difetti.

La terapia di combinazione precoce è un requisito biologico, non solo una scelta clinica, per arrestare la progressione.

Eterogeneità del DMT2.
Oltre il Concetto di "One Size Fits All"

- Il DMT2 è una patologia estremamente eterogenea per eziopatogenesi.
- I meccanismi iperglicemizzanti variano significativamente tra i pazienti.
  - Ridotta secrezione insulinica e insulino-resistenza epatica e muscolare.
  - Eccessiva secrezione di glucagone e aumento del riassorbimento renale di glucosio.
- Necessità di terapie che agiscano simultaneamente su più meccanismi.
- La sfida è identificare chi risponde meglio a specifici trattamenti (medicina di precisione).

The «reality»

- Stepwise therapy is the traditional approach for newly diagnosed type 2 diabetes, but often involves clinical inertia and delayed intensification.
- Clinical inertia, defined as the failure to intensify therapy when indicated, is pervasive in primary care settings, resulting in prolonged periods of hyperglycemia
- Studies have demonstrated that patients often remain on failing monotherapy for years before treatment intensification occurs, during which time irreversible microvascular and macrovascular damage may progress

Profilo delle classi farmacologiche

Classe	Efficacia HbA1c	Rischio Ipoglicemia	Effetto Peso	Protezione CV/Renale
SGLT2-i	Alta	Basso	Calo ponderale	Dimostrata
GLP-1 RA	Altissima	Basso	Calo ponderale	Dimostrata
DPP4-i	Intermedia	Basso	Neutro	Neutra/Sicura
Insulina	Altissima	Alto	Aumento	Neutra

SGLT2-i e GLP-1 RA offrono una potente riduzione glicemica accoppiata a benefici d'organo, superando i limiti storici della terapia.

Medicina di Precisione: Guidati dal Fenotipo



Alto Rischio CV
Scompenso Cardiaco
Nefropatia

→ **SGLT2-i**



Obesità Severa
Necessità di forte calo ponderale

→ **GLP-1 RA**



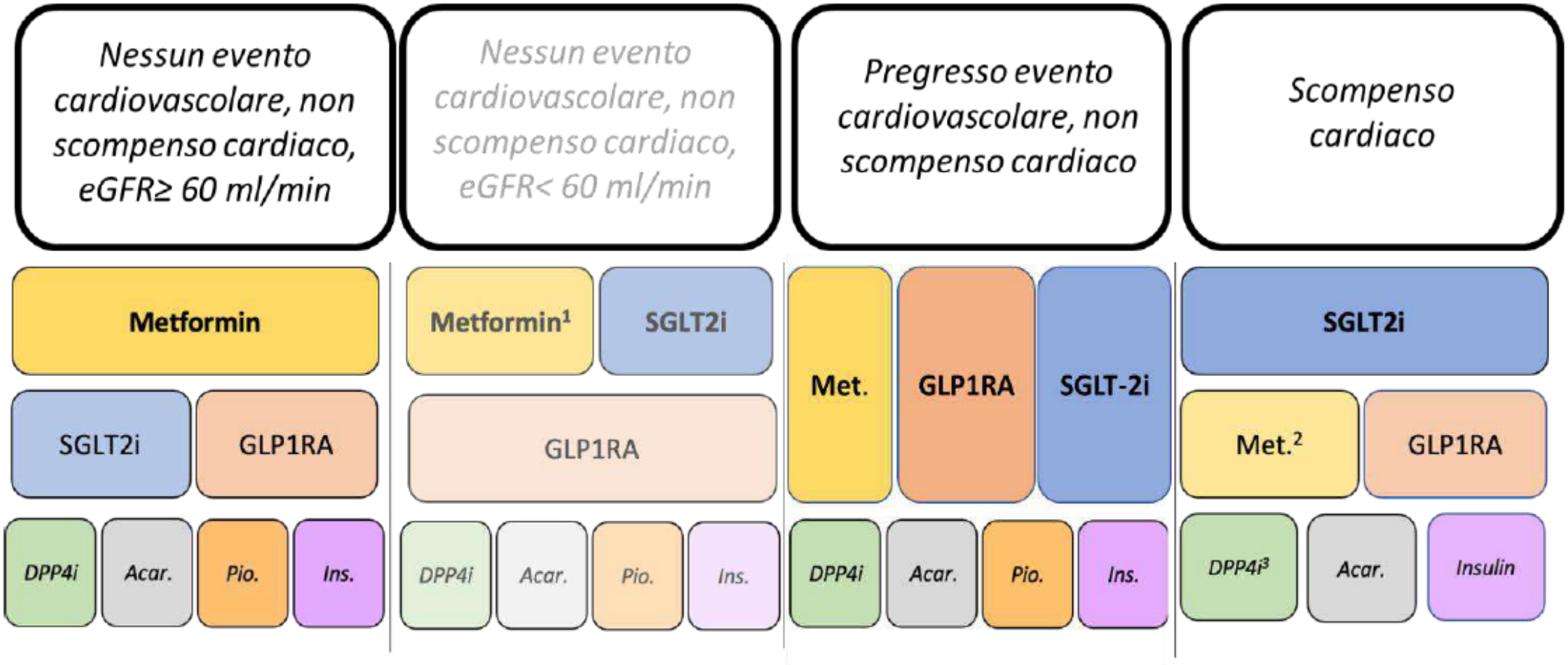
Fragilità
Anziano
Rischio ipoglicemia critico

→ **DPP4-i**

La cura ‘One Size Fits All’ è superata. Il fenotipo clinico del paziente detta la combinazione farmacologica per massimizzare il target e minimizzare i rischi

NotebookLM

Linea Guida SID e AMD



[1]*Se la metformina non è controindicata per ridotto eGFR.*
[2]*Se la metformina non è controindicata per ridotta funzione cardiaca.*
[3]*Eccetto saxagliptin che non è indicato in caso di scompenso cardiaco.*
La raccomandazione sui pazienti con eGFR< 60ml/min è debole per carenza di studi clinici effettuati su questa popolazione
Si raccomanda la deprescrizione di sulfanilurre e glinidi

Aggiornamento 23 febbraio 2023

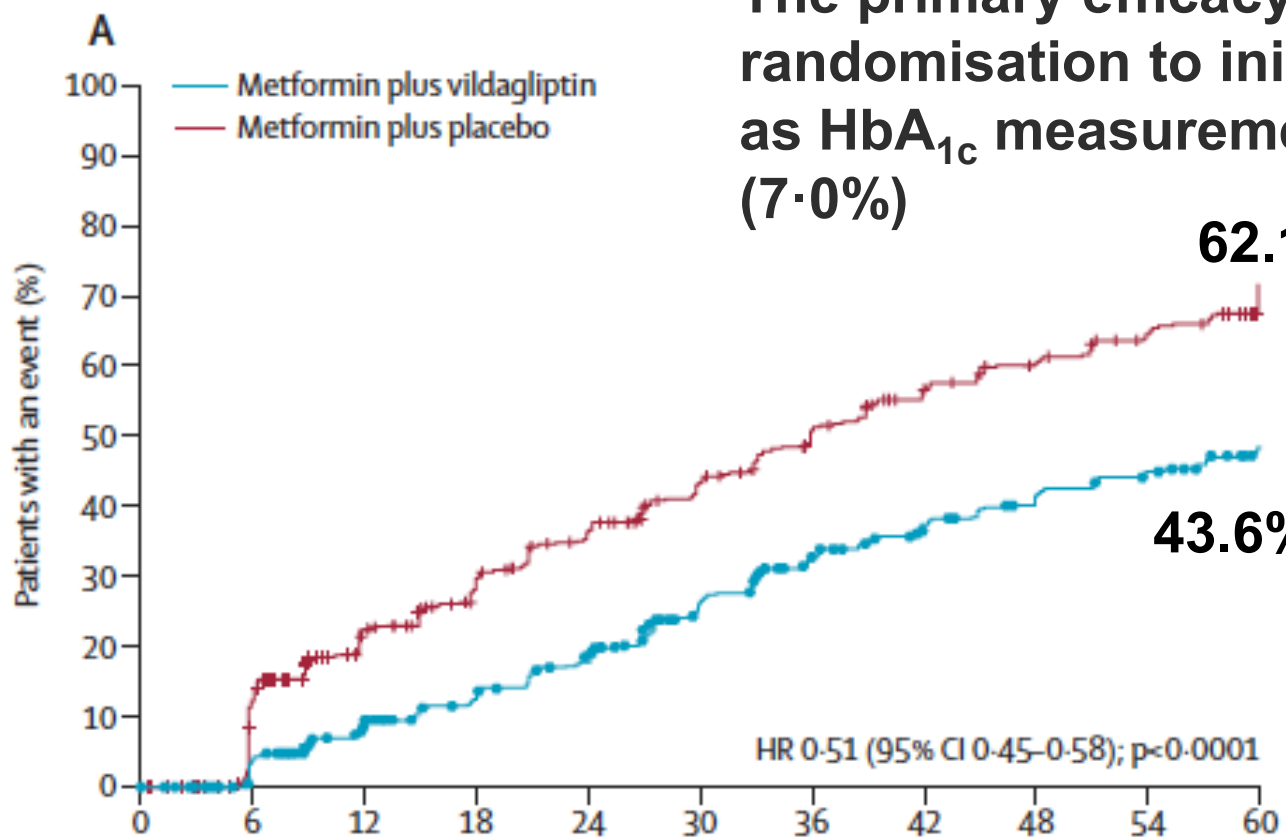
C’è un Razionale per la Terapie di Combinazione PRECOCE?

- Agire simultaneamente su diversi difetti fisiopatologici.
- Ridurre la tossicità del glucosio e migliorare la funzione beta-cellulare.
- Utilizzo di dosi sub-massimali per minimizzare gli effetti avversi.

Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial

David R Matthews, Päivi M Paldánius, Pieter Proot, YannTong Chiang, Michael Stumvoll, Stefano Del Prato, for the VERIFY study group

The primary efficacy endpoint was the time from randomisation to initial treatment failure, defined as HbA_{1c} measurement of at least 53 mmol/mol (7·0%)



62.1%

43.6%

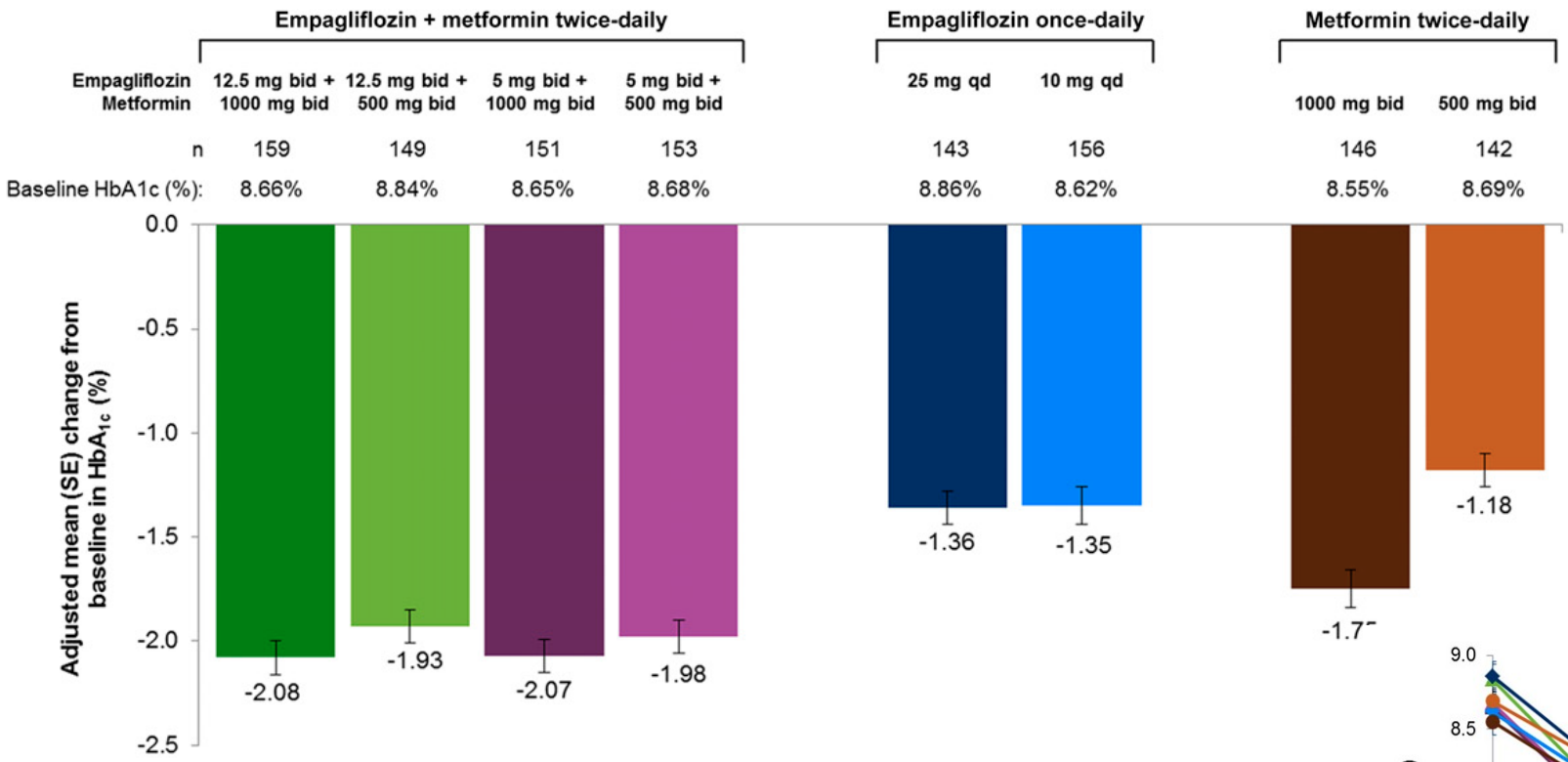
- 49% (hazard ratio 0.51; 95% CI 0.45–0.58; p<0.0001)

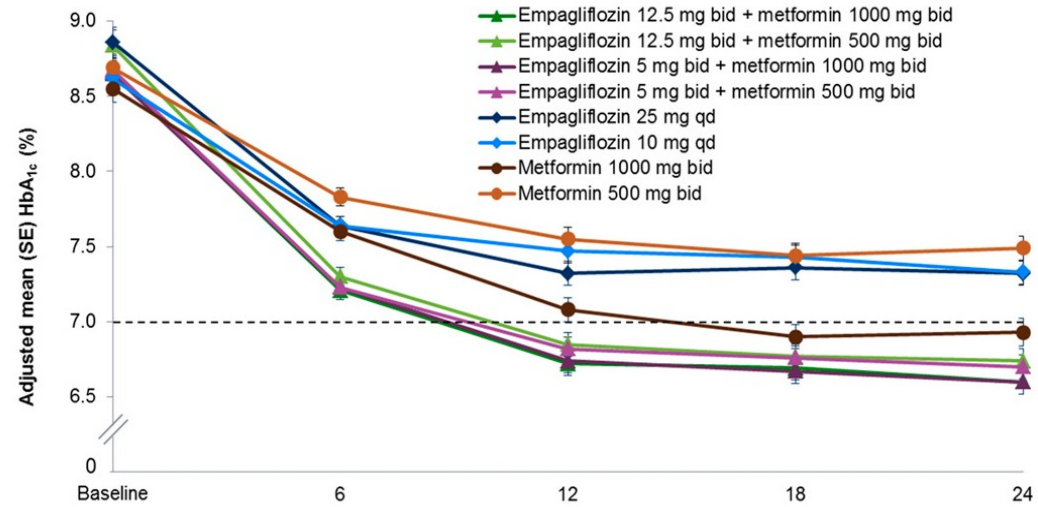
2001 participants

Initial Combination of Empagliflozin and Metformin in Patients With Type 2 Diabetes

Samy Hadjadj,[1] Julio Rosenstock,[2] Thomas Meinicke,[3] Hans J. Woerle,[4] and Uli C. Broedl[4]

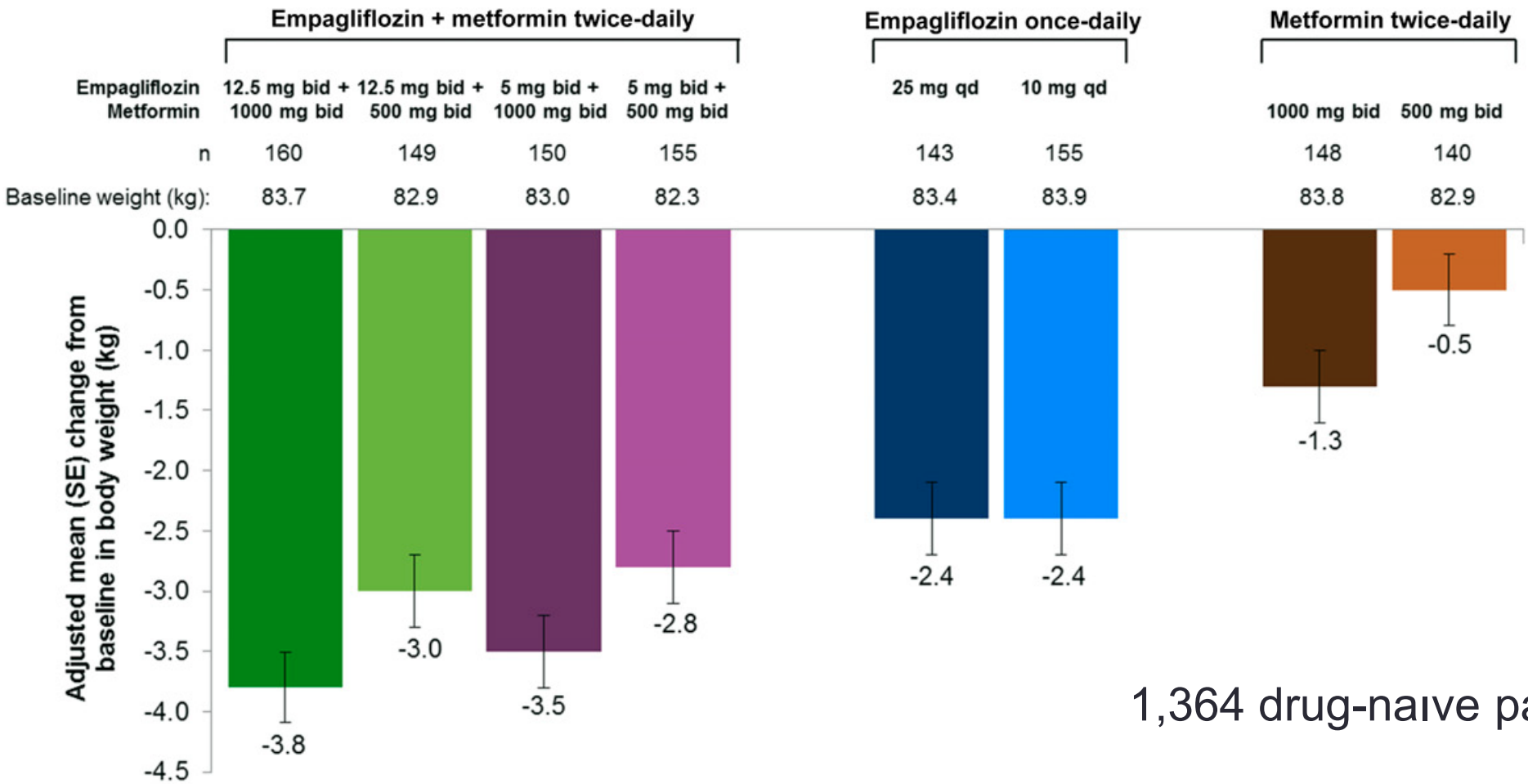
Diabetes Care 2016;39(10):1718–1728





The study randomized 1,364 drug-naıve patients (HbA1c >7.5 to £12% [>58 to £108 mmol/mol])

Changes in weight: change from baseline in weight at week 24 in randomized groups



1,364 drug-naive patients

Diabetes Care 2016;39(10):1718–1728

Early Combination Therapy vs Stepwise Escalation

in Newly Diagnosed Type 2 Diabetes: A Meta-Analysis

11 Studies | 24,364 Participants | PRISMA 2020 Compliant

Naseem E et al Canadian Journal of Diabetes 2026

Early Combination Therapy

2+ agents at diagnosis

Metformin + SGLT2i/GLP-1/DPP-4i

VS

Stepwise Escalation

Metformin monotherapy

Add agents when needed

KEY OUTCOMES

HbA1c
-0.49%

Durability
HR 0.51

B-cell funct.
preserved

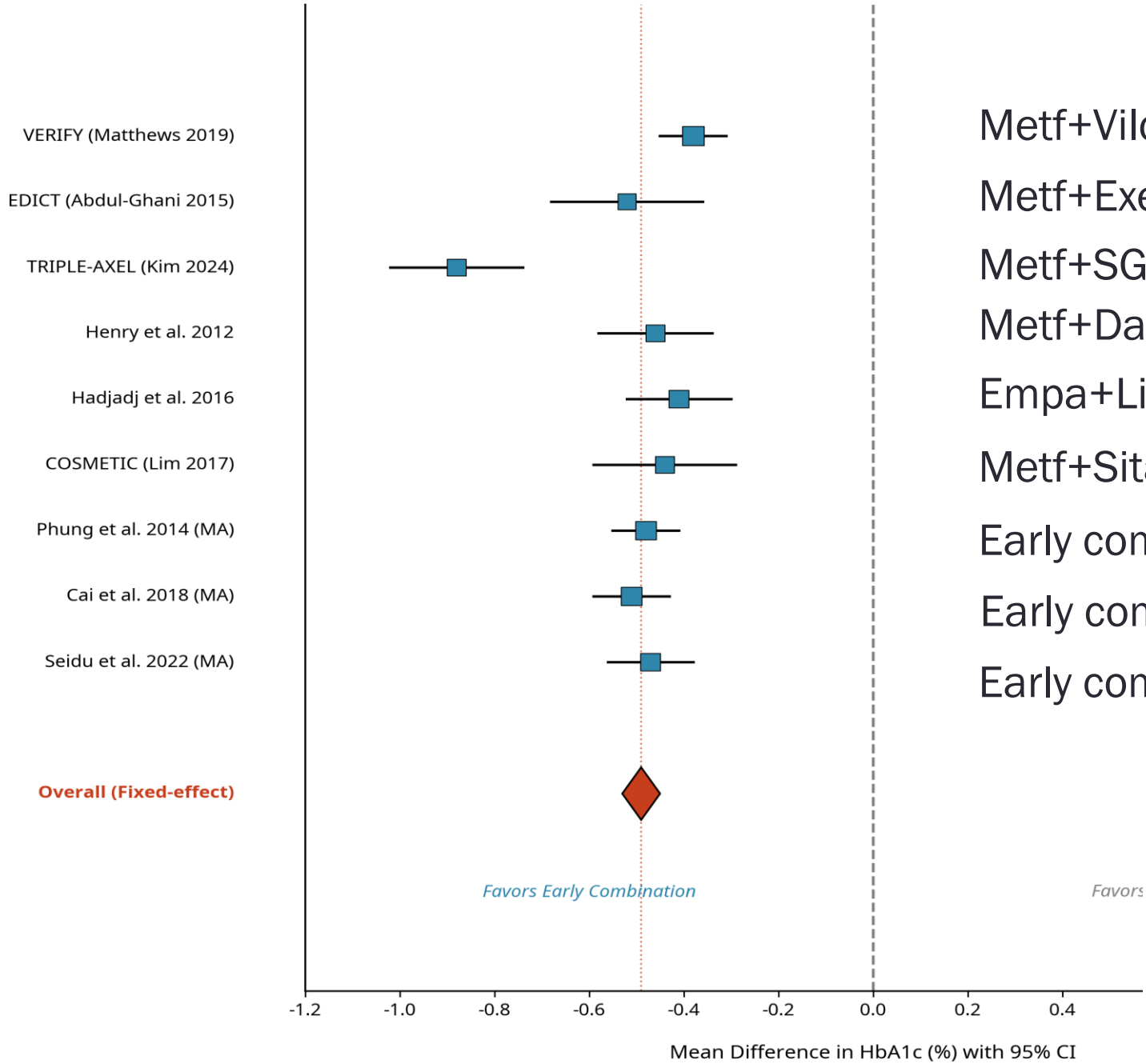
Hypoglycaemia
-7.5% lower
incidence

lower CV markers, less albuminuria, and weight

Early combination therapy provides superior glycaemic control, durability and safety

Figure 2. Forest Plot of HbA1c Reduction: Early Combination vs Stepwise Escalation

Naseem E et al Canadian Journal of Diabetes 2026



Metf+Vilda vs Metf sequential add-on

Metf+Exen+Pio vs Metf sequential add-on

Metf+SGLT2i+DPP4 vs Metf sequential add-on

Metf+Dapa vs Metf. monotherapy

Empa+Lina vs OAD monotherapy

Metf+Sita vs Metf. monotherapy

Early combination vs Metf. monotherapy

Early combination vs Metf. monotherapy

Early combination vs Metf. monotherapy

Early Combination Therapy versus Stepwise Escalation in Newly Diagnosed Type 2 Diabetes: A Systematic Review and Meta-Analysis of Multiple Clinical Outcomes

- Early combination therapy provides superior glycemic control vs. stepwise escalation.
- Treatment durability is nearly doubled with an early combination approach.
- Early combination therapy preserves beta-cell function, unlike stepwise therapy.
- This approach supports disease modification, not just symptomatic control.
- Early combination therapy is associated with lower hypoglycemia and weight gain.

Naseem E et al Canadian Journal of Diabetes 2026

Type 2 diabetes in adults: management

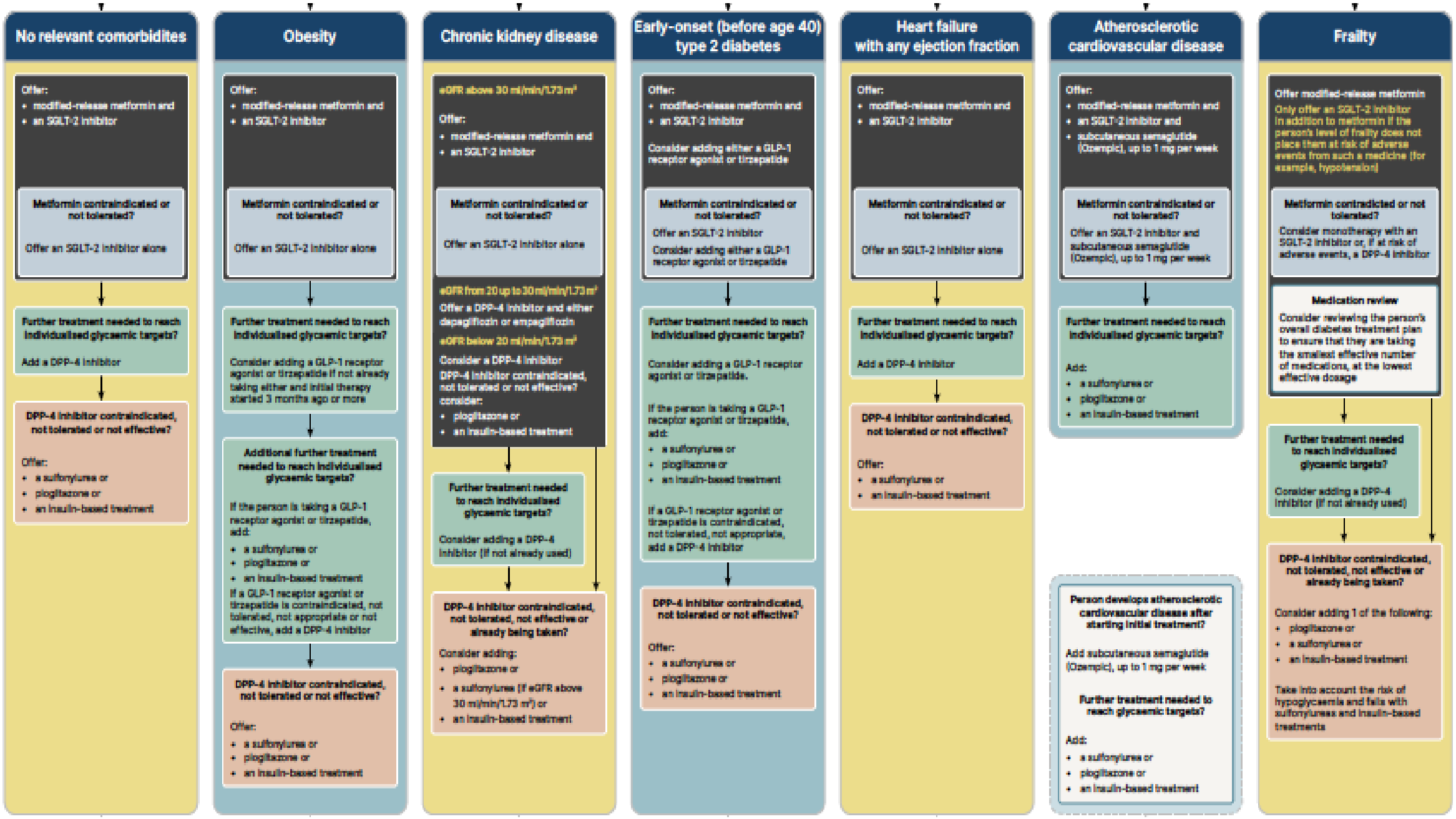
NICE guideline | NG28 | Published: 02 December 2015 | Last updated: 18 February 2026

- **1.13 People with type 2 diabetes and no relevant comorbidities**
- 1.13.1
- For adults with type 2 diabetes and no relevant comorbidity, offer:
  - modified-release metformin, and
  - an SGLT-2 inhibitor. **[2026]**

- If metformin is contraindicated or not tolerated, offer monotherapy with an SGLT-2 inhibitor. **[2026]**

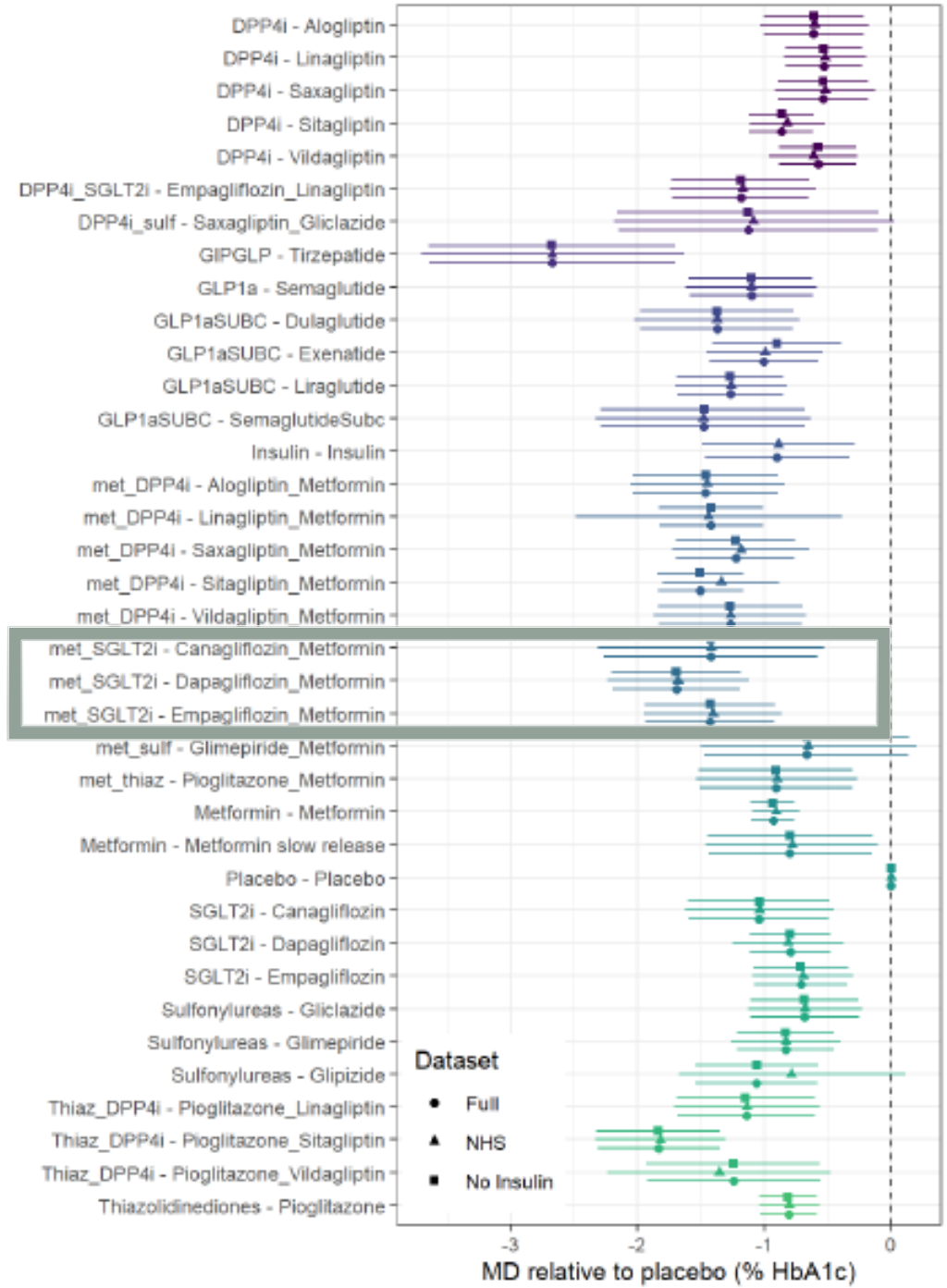
Type 2 diabetes in adults: choosing medicines for first line and further treatment

NICE 2026



Metanalysis HbA1c

NICE 2026



Treatment effects as mean differences in units of % HbA1c

Class	Treatment	Mean difference in % HbA1c vs metformin Mean (95% CrI)	Mean difference in % HbA1c vs placebo Mean (95% CrI)
DPP4-inhibitor with metformin	Alogliptin with Metformin	-0.53 (-1.10, 0.04)	-1.46 (-2.04, -0.89)
	Linagliptin with Metformin	-0.49 (-0.89, -0.09)	-1.42 (-1.83, -1.01)
	Saxagliptin with Metformin	-0.30 (-0.75, 0.16)	-1.23 (-1.70, -0.76)
	Sitagliptin with Metformin	-0.57 (-0.91, -0.24)	-1.50 (-1.84, -1.17)
	Vildagliptin with Metformin	-0.34 (-0.88, 0.21)	-1.27 (-1.83, -0.70)
SGLT2i with DPP4i	Empagliflozin with Linagliptin	-0.26 (-0.80, 0.28)	-1.19 (-1.72, -0.65)
DPP4i with sulfonylurea	Saxagliptin with Gliclazide	-0.20 (-1.21, 0.82)	-1.13 (-2.15, -0.11)
SGLT2-inhibitor	Canagliflozin	-0.11 (-0.69, 0.47)	-1.04 (-1.59, -0.49)
	Dapagliflozin	0.13 (-0.20, 0.47)	-0.80 (-1.11, -0.48)
	Empagliflozin	0.22 (-0.16, 0.59)	-0.71 (-1.08, -0.34)
SGLT2-inhibitor with metformin	Canagliflozin with Metformin	-0.49 (-1.36, 0.37)	-1.42 (-2.27, -0.58)
	Dapagliflozin with Metformin	-0.76 (-1.26, -0.27)	-1.69 (-2.20, -1.19)
	Empagliflozin with Metformin	-0.50 (-0.99, 0.00)	-1.43 (-1.94, -0.92)
GLP1 agonists	Dulaglutide	-0.44 (-1.06, 0.16)	-1.37 (-1.98, -0.77)
	Exenatide	-0.08 (-0.51, 0.35)	-1.01 (-1.44, -0.58)
	Liraglutide	-0.34 (-0.76, 0.09)	-1.27 (-1.69, -0.85)
	Semaglutide (oral)	-0.17 (-0.68, 0.34)	-1.10 (-1.59, -0.61)
	Semaglutide (subcutaneous)	-0.55 (-1.38, 0.27)	-1.48 (-2.29, -0.68)
GIPGLP	Tirzepatide	-1.74 (-2.72, -0.77)	-2.67 (-3.64, -1.70)
Sulfonylureas	Gliclazide	0.25 (-0.17, 0.67)	-0.68 (-1.10, -0.26)
	Glimepiride	0.10 (-0.28, 0.47)	-0.83 (-1.21, -0.45)
	Glipizide	-0.13 (-0.62, 0.35)	-1.06 (-1.55, -0.58)
Sulfonylurea with metformin	Glimepiride with Metformin	0.27 (-0.54, 1.07)	-0.66 (-1.47, 0.14)

NICE 2026

NICE 2026 rationale for first-line metformin + SGLT2 inhibitor

- Overall, network and pairwise meta-analyses comparing antidiabetic therapies showed that **therapy combining metformin with an SGLT-2 inhibitor vs. any other therapy combining metformin with 1 other medicine, and metformin alone:**
  - Has superior HbA1c reduction, weight loss and cardiovascular outcomes versus metformin alone or any other metformin-based dual therapy
  - Reduces CV death, MI, stroke and HF hospitalisation
  - Provides renal protection, including lower risk of end-stage kidney disease
  - Benefits outweigh risks for most patients

- Therefore it is considered the **"most clinically effective therapy option"** and recommended as **standard initial treatment**

Improving outcomes with early and intensive metabolic control in patients with type 2 diabetes: a long-term modeling analysis of clinical and cost outcomes in Italy

Arietti P et al. Journal of Diabetes & Metabolic Disorders (2025)

Table 3 Potential clinical benefits and cost savings of EIMC versus conventional metabolic control in Italy over the next 10 years for patients newly diagnosed with type 2 diabetes in 2021

		Undiscounted life expectancy (years)	Discounted life expectancy (years)	Quality-adjusted life expectancy (years)	Direct cost (EUR)	Total costs (EUR)
Patient level	EIMC	8.81	7.80	6.14	25,075	28,344
	Standard care	8.76	7.76	5.99	26,943	30,625
	Difference	**+0.05**	**+0.04**	**+0.15**	**−1,868**	**−2,281**
Population level	EIMC	1,906,637	1,688,056	1,328,803	5.427 million	6.134 million
	Standard care	1,895,816	1,679,399	1,296,340	5.831 million	6.628 million
	Difference	**+10,821**	**+8,657**	**+32,463**	**−404.3 million**	**−493.6 million**

Population size is based on data of newly diagnosed patients with type 2 diabetes in 2021

Oltre la glicemia: azzerare il rischio residuo (Studio Steno-2)



Curare solo la glicemia è insufficiente. L'intervento multifattoriale intensivo è l'unico scudo comprovato contro la mortalità.

NotebookLM

Conclusioni

- Agire subito: la memoria metabolica inizia dal giorno 1. L'inerzia terapeutica e l'approccio stepwise si associano a peggiori outcomes metabolici e clinici
- Target rigorosi: obiettivi di HbA1c molto ambiziosi (<5.7-6%). I farmaci lo permettono senza rischio ipoglicemico
- Terapia di combinazione: utilizzare combinazioni precocemente (o da subito), guidati dal fenotipo e dal profilo cardio-renale, migliora controllo metabolico, peso, durability, rischio CVD, complicanze