Quinto Meta Open Forum

SID Società Italiana di Diabetologia fondata nel 1964

SURPASS-CVOT

Moderatori: Nicola Napoli, Giorgio Sesti

08.30 Perché tirzepatide dovrebbe essere superiore
Stefano Del Prato

08.50 Discussione

09.00 Perché tirzepatide non è risultata superiore
Gian Paolo Fadini

Perché non è risultata superiore?

G. P. Fadini
Dip. di Medicina
Università di Padova

Dichiarazione conflitto di interessi

Il prof. Gian Paolo FADINI dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Astrazeneca
- Boehringer
- Lilly
- Sanofi
- Giudotti
- 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.).

My two cents…

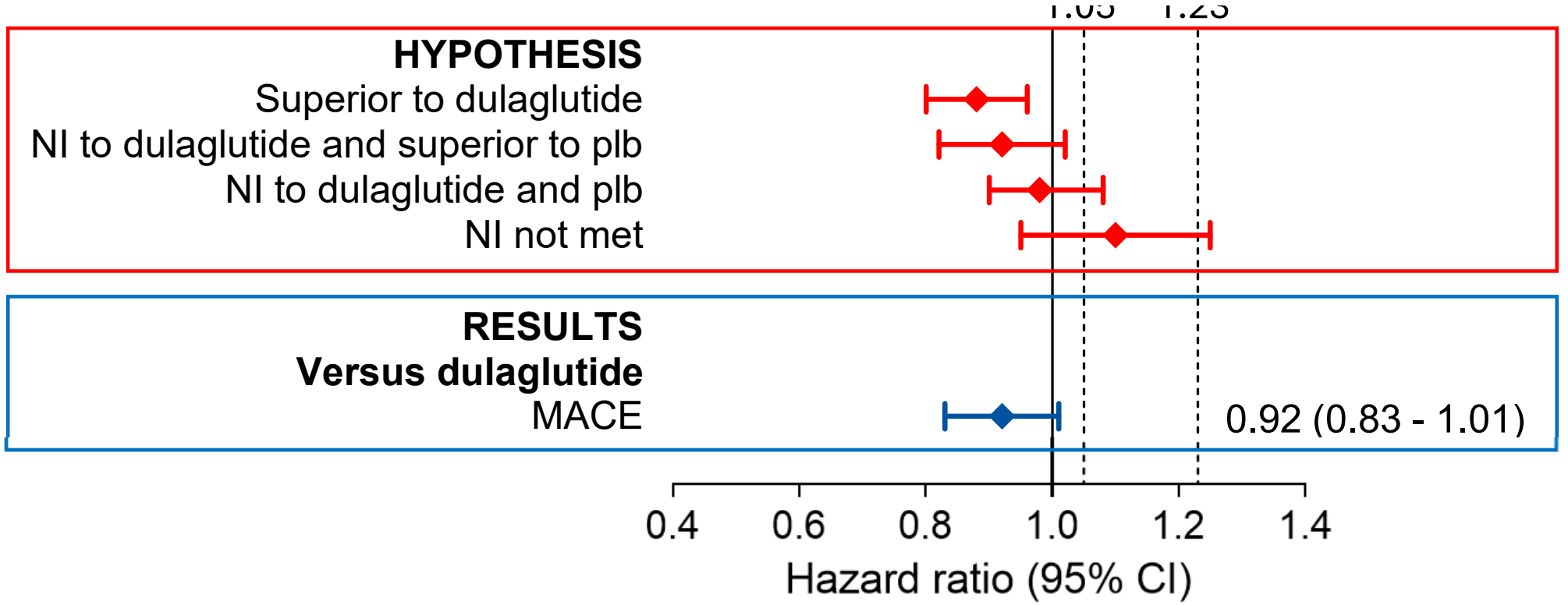
Diabetes Ther (2025) 16:1893–1898
https://doi.org/10.1007/s13300-025-01784-x

COMMENTARY

Can Dual Incretin Receptor Agonists Exert Better Cardiovascular Protection than Selective GLP-1 Receptor Agonists? Highlights from SURPASS-CVOT

Gian Paolo Fadini

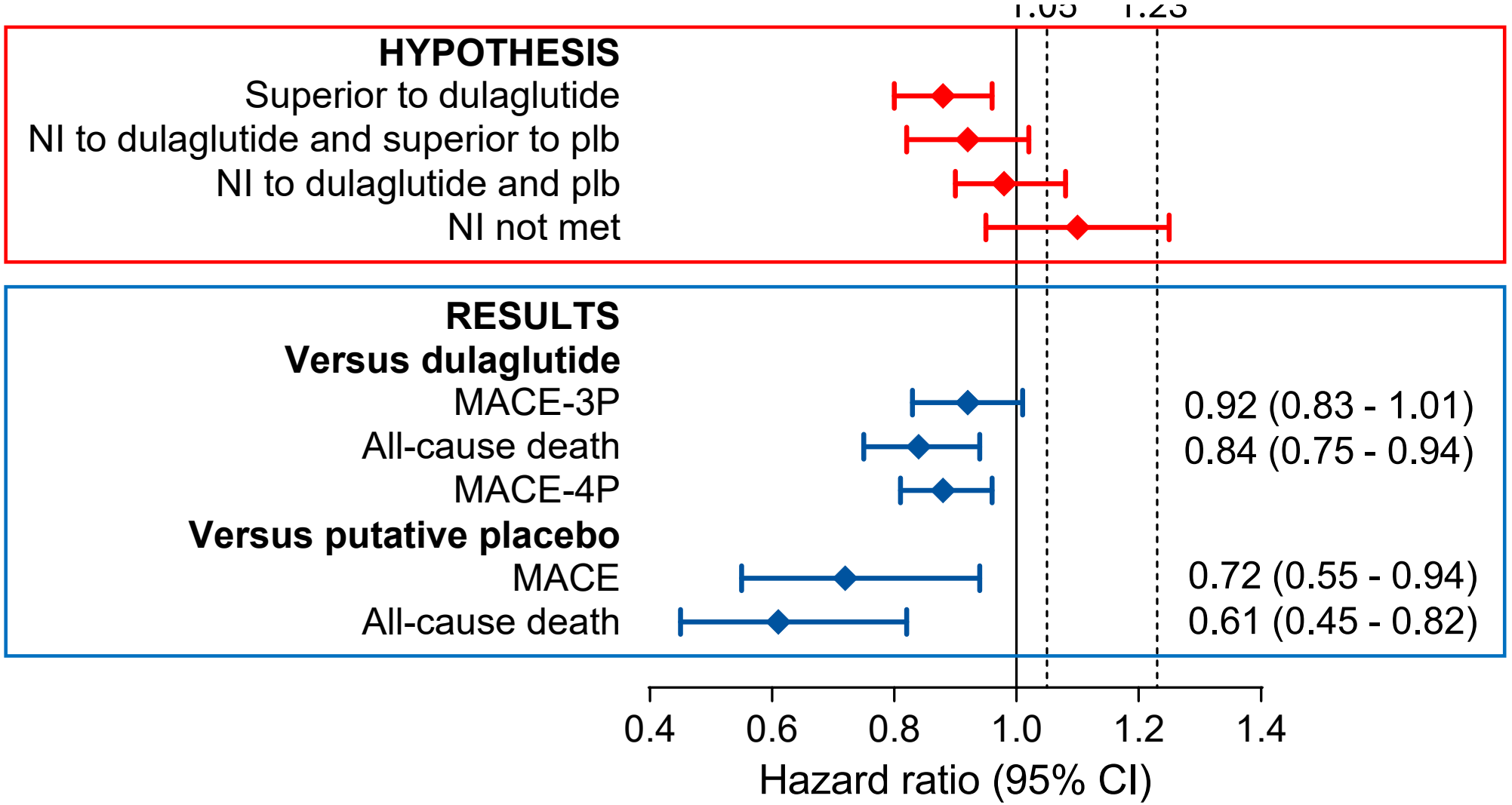
Non è risultata superiore?



Spostando 10 eventi dei 1663 dal braccio tirzepatide al braccio dulaglutide, l'approssimazione sui conteggi fornirebbe
HR 0.91 (95.3% CI 0.82–1.00)
p (two-sided) ≈ 0.044

Fadini, Diabetes Therapy 2025

Non è «veramente» superiore?



Fadini, Diabetes Therapy 2025

Missed superiority on MACE-3P

Why outstanding benefits on HbA1c, weight, eGFR did not translate into greater CV protection?

Let's explain 1.01 (10 events)

1. It takes longer
2. SGLT2i drop-in imbalance
3. Baseline risk different than expected
4. Dula more protective than expected
5. What GIPRA adds to CV protection?
6. Occult mechanism(s) against CV benefit

Missed superiority on MACE-3P

Why outstanding benefits on HbA1c, weight, eGFR did not translate into greater CV protection?

1. It takes longer

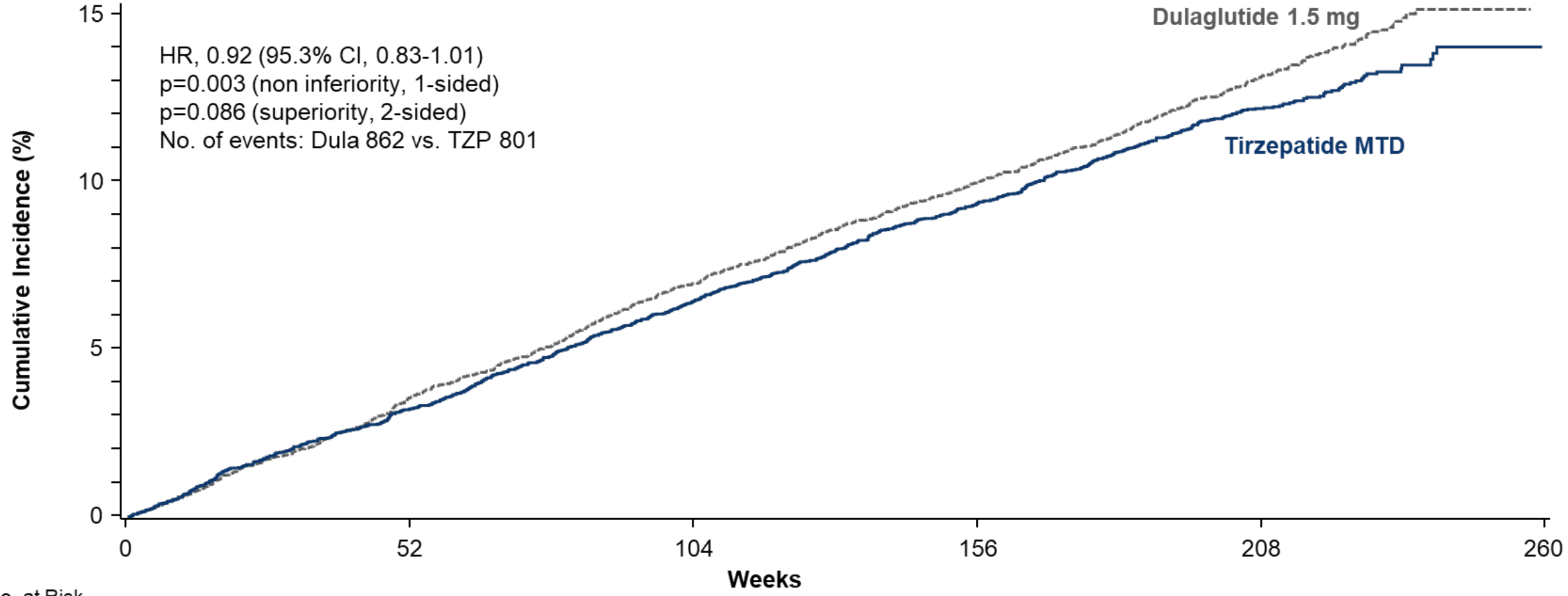
Median f-up 4 years should be sufficient to see CV benefits from GLP-1RA…

SUSTAIN-6	2.1 y
LEADER	3.8 y
SOUL	4.1 y
REWIND	5.4 y

… but it may take longer for Δ*HbA1c* to translate into CV protection
(UKPDS, ACCORD-ION, ADVANCE-ON)

Missed superiority on MACE-3P

1. It takes longer



No. at Risk						
TZP MTD	6586	6309	6029	5703	3305	0
Dula 1.5 mg	6579	6267	5954	5618	3226	0

Nicholls SJ,. N Engl J Med. 2025 Dec 18;393(24):2409-2420.

Missed superiority on MACE-3P

Why outstanding benefits on HbA1c, weight, eGFR did not translate into greater CV protection?

2. SGLT2i drop-in imbalance

Baseline ~30% in both groups

Due to ΔHbA1c, more SGLT2i were initiated after randomization in the dula arm

→ could improve CV outcomes in the dula arm

→ does this impinge upon CV efficacy of GLP-1RA? **No....**

Hazard ratios estimated in a time-dependent Cox regression with SGLT2i use (yes vs. no) during trial as a time-dependent covariate

SOUL

Oral Semaglutide

Outcome	Oral semaglutide (n=4825)	Placebo (n=4825)	Treatment	
	n (%)	n (%)	HR (95% CI)	p-value
MACE	579 (12·0)	668 (13·8)	**0·84 (0·75; 0·94)**	**0·0026**
CV death	301 (6·2)	320 (6·6)	0·91 (0·78; 1·06)	0·23
Non-fatal MI	191 (4·0)	253 (5·2)	**0·75 (0·62; 0·91)**	**0·0027**
Non-fatal stroke	144 (3·0)	161 (3·3)	0·87 (0·70; 1·09)	0·24

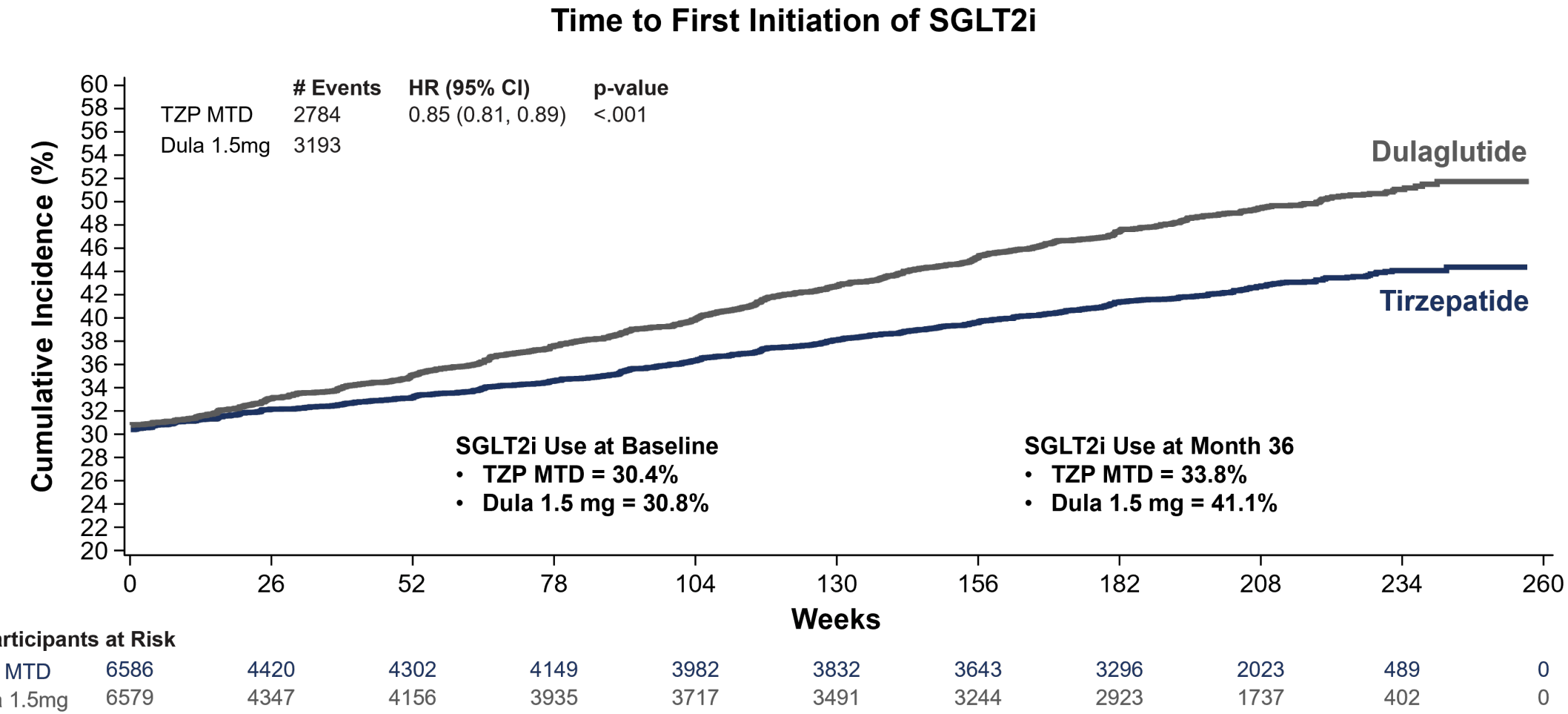
An **inverse probability weighting analysis** of time to first MACE, which more rigorously try to balance the initiation and discontinuation of SGLT2i use during trial between the randomised treatment, **the results was consistent with time-dependent Cox regressions**

With the limitations given for analyses including post-randomized variables, **the analyses on MACE outcomes for any SGLT2is use during the trial suggest the oral semaglutide reduce risk of MACE vs. placebo independently of SGLT2i use**

Missed superiority on MACE-3P

Why outstanding benefits on HbA1c, weight, eGFR did not translate into greater CV protection?

2. SGLT2i drop-in imbalance



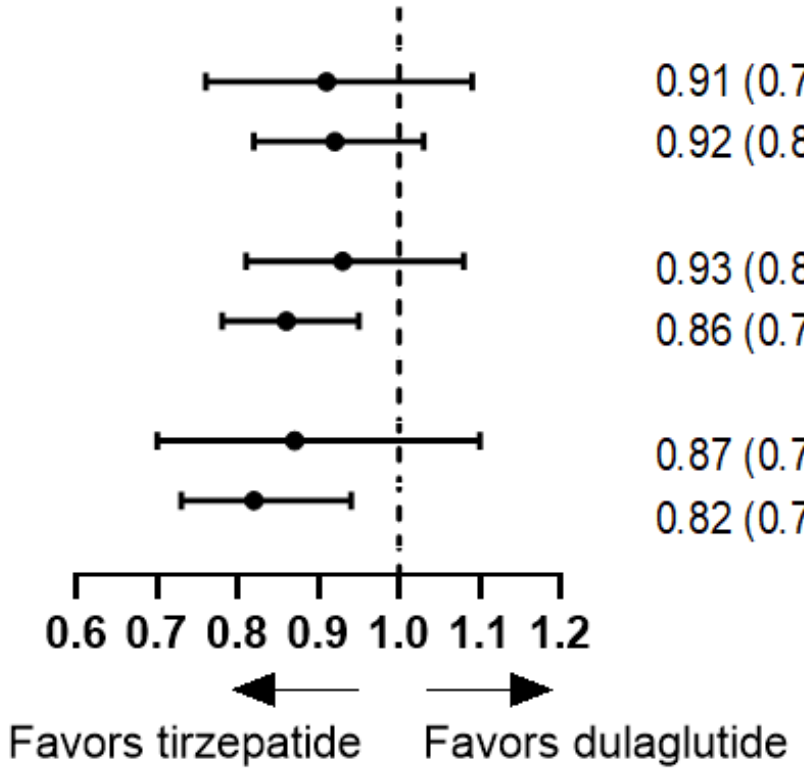
American Heart Association (AHA); New Orleans, LA; November 7-10, 2025

Missed superiority on MACE-3P

Why outstanding benefits on HbA1c, weight, eGFR did not translate into greater CV protection?

2. SGLT2i drop-in imbalance

	Tirzepatide MTD n/N (%)	Dulaglutide 1.5 mg n/N (%)	Hazard Ratio (95% CI)
MACE 3			
SGLT2i use at BL: yes	231/2002 (11.5)	254/2025 (12.5)	0.91 (0.76, 1.09)
SGLT2i use at BL: no	570/4584 (12.4)	608/4554 (13.4)	0.92 (0.82, 1.03)
MACE 4			
SGLT2i use at BL: yes	348/2002 (17.4)	374/2025 (18.5)	0.93 (0.81, 1.08)
SGLT2i use at BL: no	741/4584 (16.2)	843/4554 (18.5)	0.86 (0.78, 0.95)
All-cause death			
SGLT2i use at BL: yes	140/2002 (7.0)	161/2025 (8.0)	0.87 (0.70, 1.10)
SGLT2i use at BL: no	426/4584 (9.3)	508/4554 (11.2)	0.82 (0.73, 0.94)



Missed superiority on MACE-3P

Why outstanding benefits on HbA1c, weight, eGFR did not translate into greater CV protection?

3. Different baseline risk

No…

MACE rates in the Dula arm was exactly as expected (3.5% / y)

Lower than in typical Plb arms

Powered for a 15% relative risk reduction

→ underpowered in case the true effect is <15% RRR

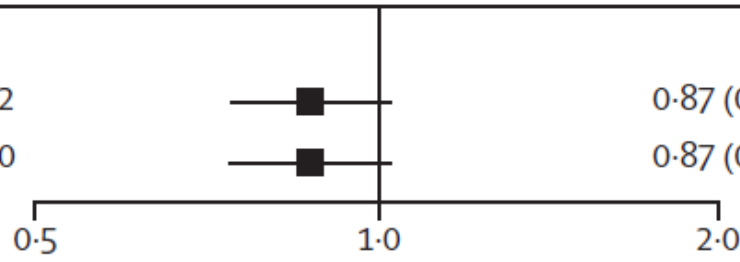
Missed superiority on MACE-3P

Why outstanding benefits on HbA1c, weight, eGFR did not translate into greater CV protection?

4. Dula was more protective than expected

HR in REWIND = 0.88 in both subgroups w/wo ASCVD

	Dulaglutide		Placebo		Hazard ratio (95% CI)	$p_{interaction}$
	Events/patients (%)	Incidence (per 100 person–years)	Events/patients (%)	Incidence (per 100 person–years)		
History of cardiovascular disease*						0·97
Yes	280/1560 (17·9%)	3·7	315/1554 (20·3%)	4·2	0·87 (0·74–1·02)	
No	277/3093 (8·9%)	1·7	317/3128 (10·1%)	2·0	0·87 (0·74–1·02)	



But the ASCVD population of REWIND was different from that of SURPASS-CVOT

Estimated effect of Dula vs Plb in the SURPASS-CVOT population

HR 0.78 for MACE

HR 0.73 for CV death

Missed superiority on MACE-3P

Why outstanding benefits on HbA1c, weight, eGFR did not translate into greater CV protection?

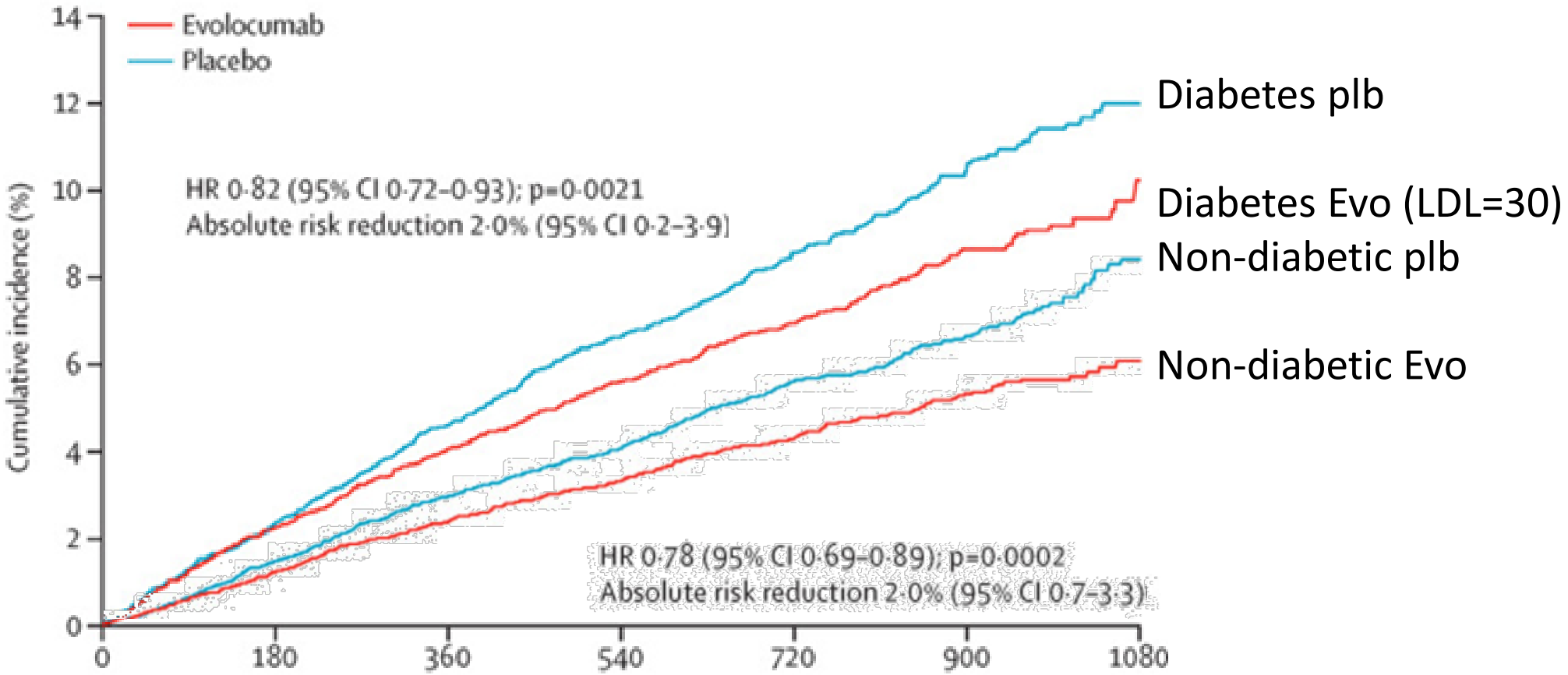
5. What GIPR agonism adds to GLP1R agonism for CV protection?

Independently from HbA1c and weight, does dual R activation protects the heart and vessels more than GLP1R activation?

- *Yes, because GIPR has different expression profiles and effects*
- *Yes, because GIPR agonism has anti-atherosclerotic effects*
- *Yes, but the effect is small(<10%)*
- *No, because the effects of GIP on atherosclerosis have been historically controversial*
- *No, because the "incretin" system is already maximally stimulated by GLP-1RA*

Missed superiority on MACE-3P

Quanto è aggredibile il rischio residuo?



Diabetes plb

Diabetes Evo (LDL=30)

Non-diabetic plb

Non-diabetic Evo

Lancet Diabetes Endocrinol. 2017 Dec;5(12):941-950.

Missed superiority on MACE-3P

Why outstanding benefits on HbA1c, weight, eGFR did not translate into greater CV protection?

6. Occult mechanism(s) in the TZP arm acting against CV benefit

… that partially neutralize the benefits of glucose and weight control

- Hypoglycemia?
- Deprescription of protective medications?
- Excess weight loss?
- What else?

Missed superiority on MACE-3P

Why outstanding benefits on HbA1c, weight, eGFR did not translate into greater CV protection?

1. It takes longer	**Maybe**
2. SGLT2i drop-in imbalance	**No**
3. Baseline risk different than expected	**No**
4. Dula more protective than expected	**Probably**
5. What GIPRA adds to CV protection?	**Unknown**
6. Occult mechanism(s) against CV benefit	**Impossible to rule out**
	… but unlikely

Reframe our expectations

Why MACE-3p?

What about MACE-4 or MACE-5?

Is non-fatal MI much more important than UA or revascularization?

Why CV mortality alone?

What about overall mortality?

Reframe our expectations

Why CV mortality alone?

What about overall mortality?

THE LANCET
Diabetes & Endocrinology

COMMENT · Volume 9, Issue 3, P131-133, March 2021

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Cancer overtakes vascular disease as leading cause of excess death associated with diabetes

Mingyang Song [a,b]

THE LANCET *Regional Health*
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Contribution of infection to mortality in people with type 2 diabetes: a population-based cohort study using electronic records

Iain M. Carey [a] · Julia A. Critchley [a,d] · Umar A.R. Chaudhry [a] · Stephen DeWilde [a] · Elizabeth S. Limb [a] · Liza Bowen [a] · et al. Show more

Reframe our expectations

	Dulaglutide (N=6579)	Tirzepatide (N=6586)	Cause Specific Hazard Ratio (95% CI)
All cause death n, (%)	669 (10.2)	566 (8.6)	**0.84 (0.75-0.94)**
Death from cardiovascular causes n, (%)	408 (6.2)	367 (5.6)	**0.89 (0.77-1.02)**
Non-cardiovascular cause death n, (%)	261 (4.0)	199 (3.0)	**0.75 (0.63-0.91)**
Infection n, (%)	138 (2.1)	78 (1.2)	**0.56 (0.42-0.74)**
Malignancy n, (%)	75 (1.1)	72 (1.1)	**0.95 (0.69-1.31)**
Trauma n, (%)	15 (0.2)	13 (0.2)	**0.86 (0.41-1.80)**
Others n, (%)	33 (0.5)	36 (0.5)	NA

Hazard ratios are derived from a Cox proportional-hazards model with treatment as a fixed effect, stratified by SGLT2 inhibitor use at baseline in the modified intention to treat population. There was no adjustment for multiplicity, and the widths of the confidence intervals should not be used in place of hypothesis testing.

Nicholls S.J. et al. *N Engl J Med*. 2025;393:2409-2420