CONGRESSO CONGIUNTO SID-AMD-SIEDP-SIE - ANIED-OSDI

"DIABETE ED OBESITA': SI PUO' INVERTIRE LA ROTTA?
Cosa abbiamo guadagnato e cosa abbiamo perso"

DM2 con malattia CV stabile: SGLT-2 e GLP-1 subito insieme?

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CONFLITTI DI INTERESSE

Il dott **Stefano Ciardullo** dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- AstraZeneca
- Boheringer Ingelheim
- Eli Lilly
- MSD
- Novonordisk

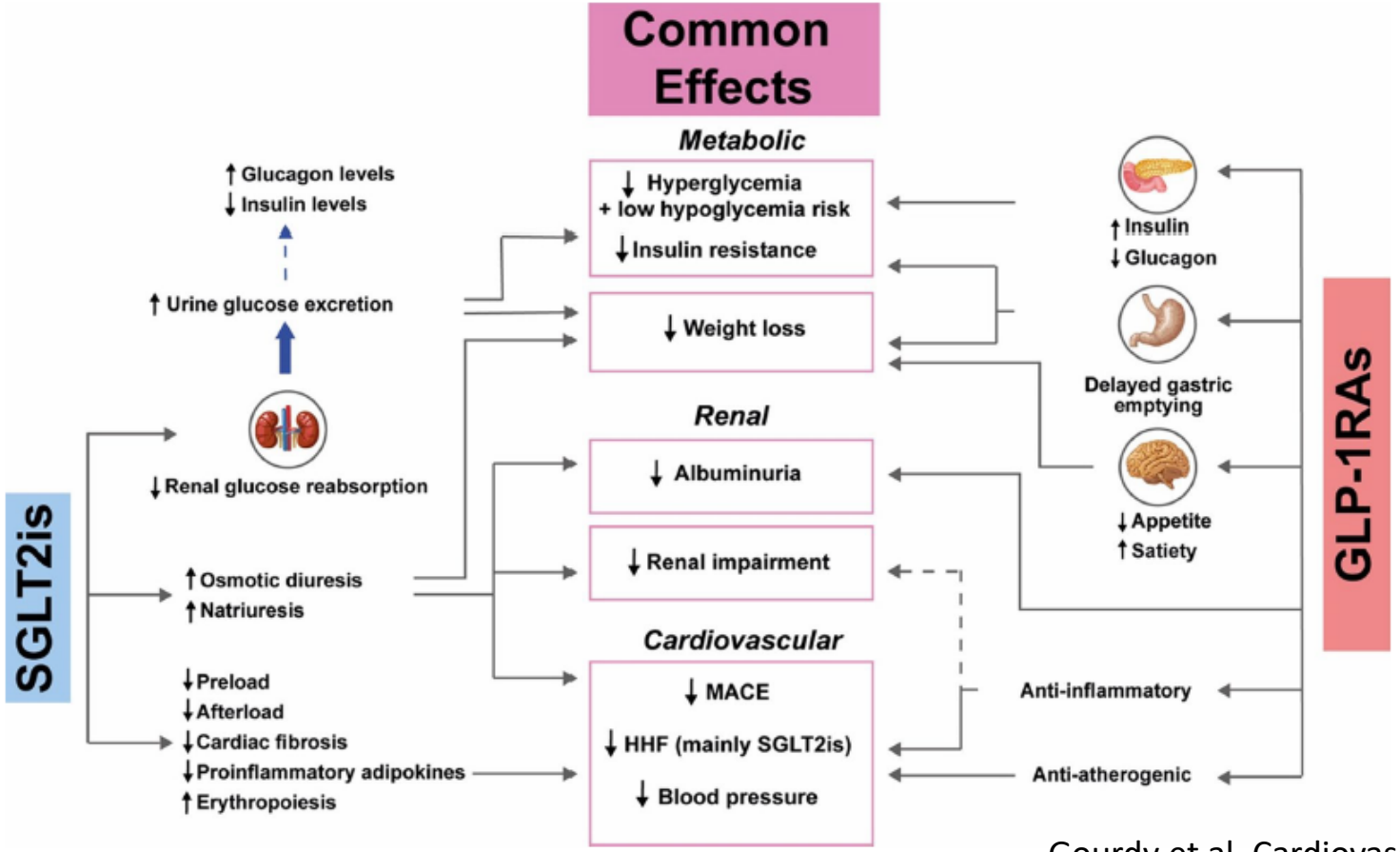
Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi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

AGENDA

- **Razionale fisiopatologico e clinico dell'associazione**
- Effetti dell'associazione sul compenso glicemico
- Effetti dell'associazione sui fattori di rischio cardiovascolare
- Effetti dell'associazione sugli eventi
- Possibili argomenti a sfavore

RAZIONALE FISIOPATOLOGICO

Since, GLP-1 RA and SGLT2i have beneficial effects through **different mechanisms of action**, it is reasonable to assume that combination therapy can have at least **complementary (or even additive / synergistic) effect** on various outcomes



Gourdy et al. Cardiovascular Diabetology (2023) 22:79

RAZIONALE CLINICO

Outcome	GLP1-RA[1]	SGLT2-i[2]	Combination[3]
MACE	↓	↓	↓↓
Myocardial infarction	↓	↔	↓
Stroke	↓↓	↔	↓↓
Heart failure	↓	↓↓	↓↓↓
Albuminuria	↓	↓↓	↓↓↓
ESRD	↔	↓	↓
All-cause mortality	↓	↓	↓↓

[1] Sattar et al. Lancet Diabetes Endocrinol 2021;9;653-62
[2] McGuire et al. JAMA Cardiology 2021;6(2):148-158
[3] Expected

AGENDA

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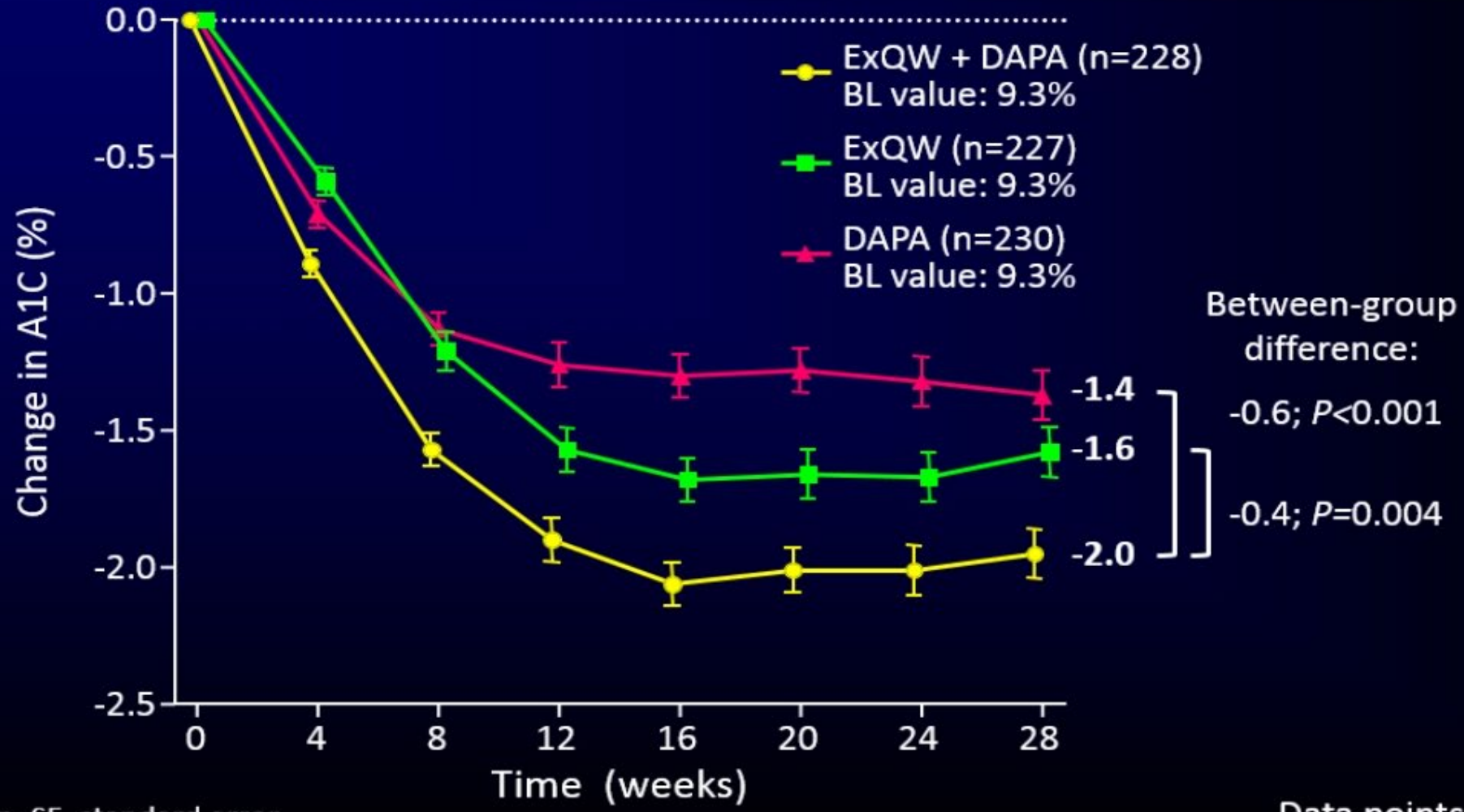
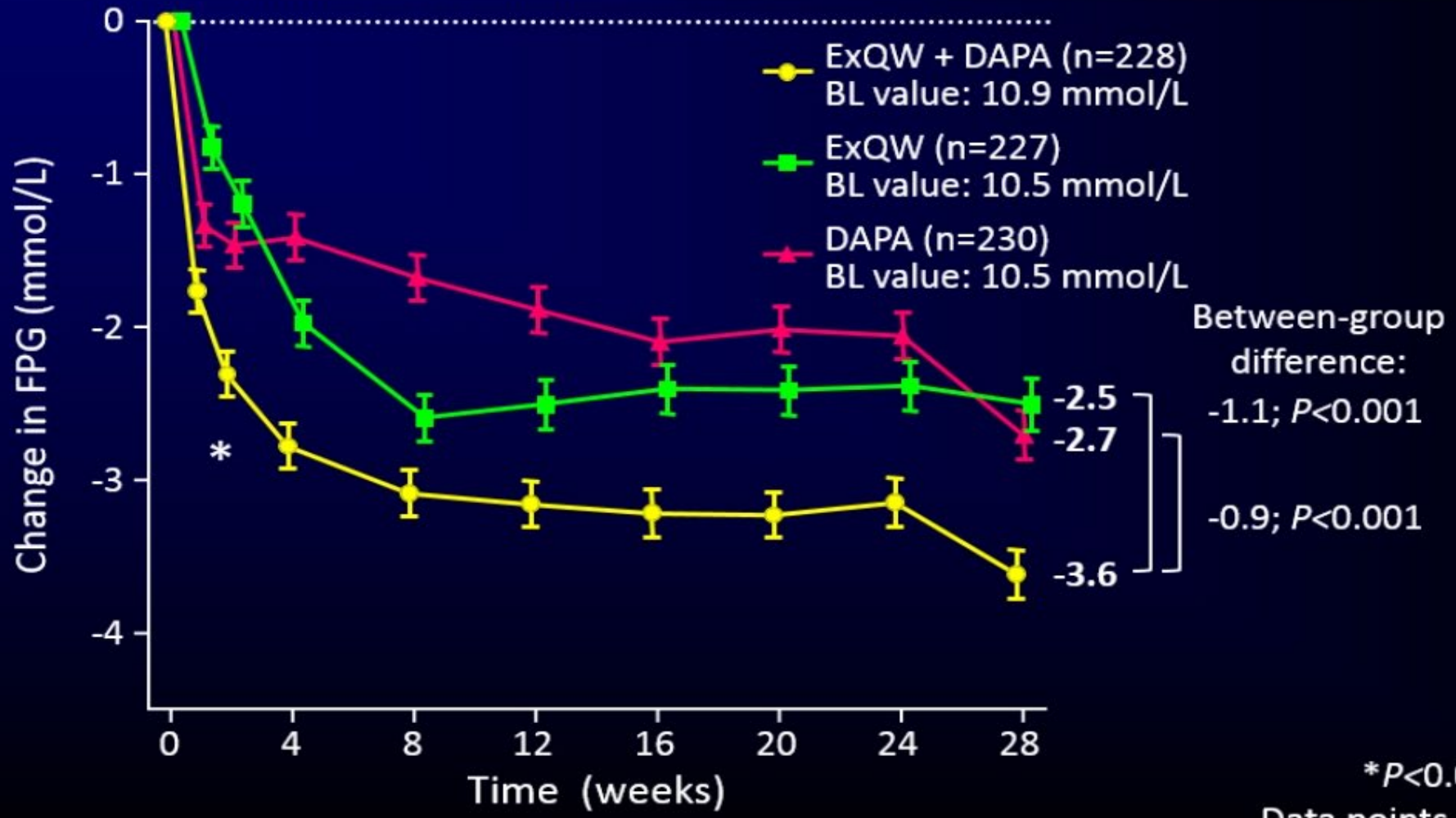
Change in A1C



BL, baseline;
LSM, least-squares mean; SE, standard error.

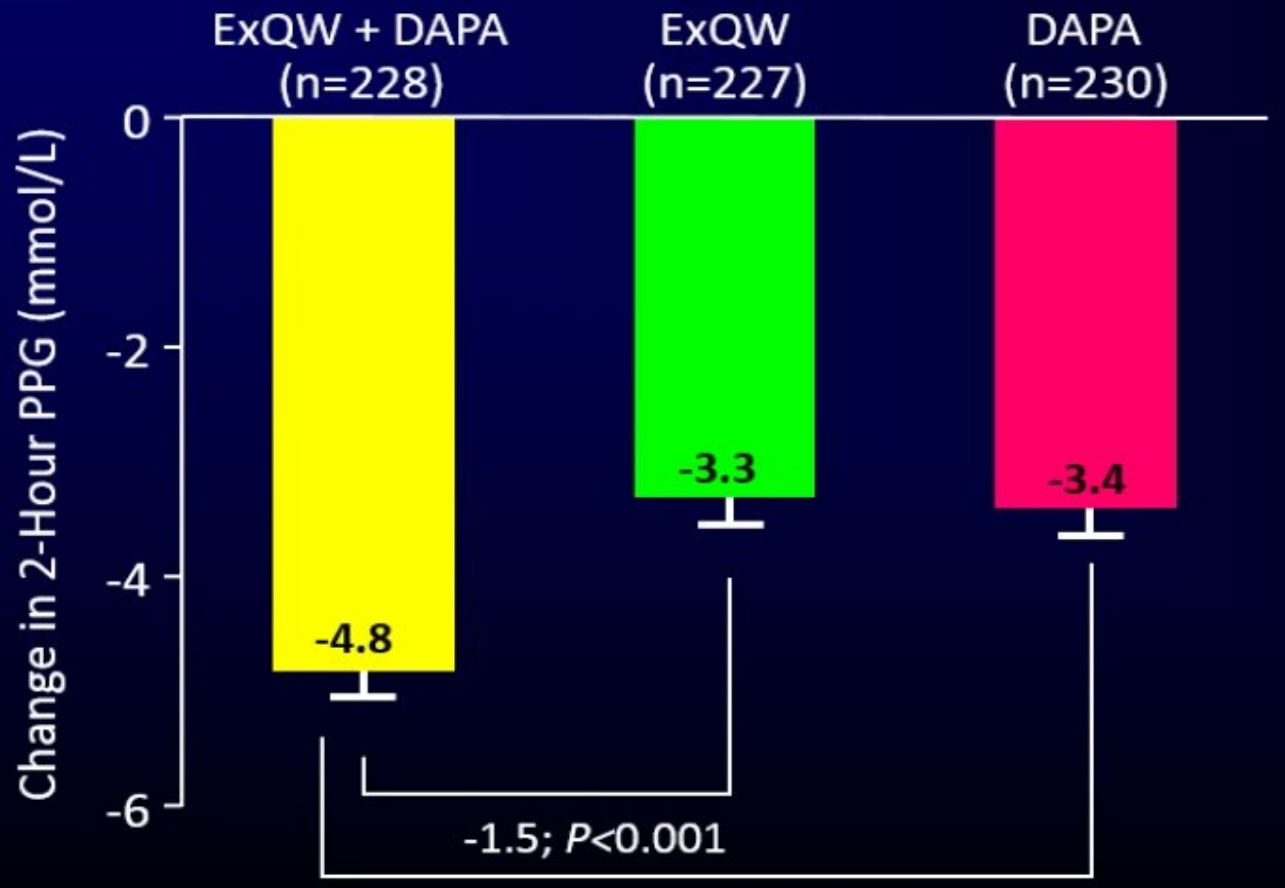
Data points are LSM ± SE

Change in Fasting Glucose



*P<0.001 vs ExQW
Data points are LSM ± SE

Change in 2-Hour Postprandial Glucose (Standardized Liquid Meal Test)



PPG, postprandial glucose.

Data points are LSM ± SE

EMOGLOBINA GLICATA

Change from baseline in HbA1c (%)

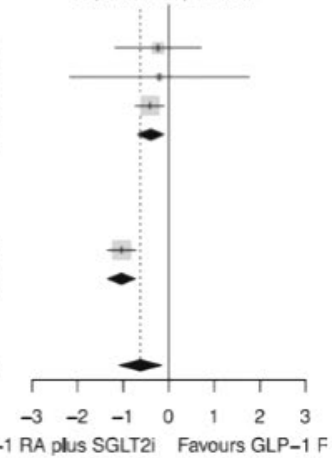
GLP-1 RA plus SGLT2i compared with:

(A) GLP-1RA

(B) SGLT2i

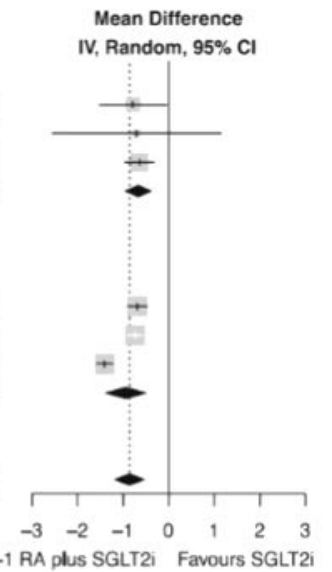
(A)

Study or Subgroup	GLP–1 RA plus SGLT2i Mean	SD	Total	GLP–1 RA Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Simultaneous initiation of GLP–1 RA plus SGLT2i								
Ali 2020[36]	−1.67	1.12	15	−1.44	1.51	15	16.3%	−0.23 [−1.18; 0.72]
Ikonomidis 2018[28]	−1.50	3.58	20	−1.30	2.68	20	5.2%	−0.20 [−2.16; 1.76]
Jabbour 2018[21]	−1.70	1.66	228	−1.29	1.81	227	39.0%	−0.41 [−0.73; −0.09]
Total (95% CI)			**263**			**262**	**60.5%**	**−0.39 [−0.69; −0.09]**
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.16$, df = 2 ($P = 0.92$); $I^2 = 0\%$								
Sequential addition of SGLT2i to GLP–1 RA								
Fulcher 2016[24]	−0.86	0.71	65	0.17	0.71	30	39.5%	−1.03 [−1.34; −0.72]
Total (95% CI)			**65**			**30**	**39.5%**	**−1.03 [−1.34; −0.72]**
Heterogeneity: not applicable								
Total (95% CI)			**328**			**292**	**100.0%**	**−0.61 [−1.09; −0.14]**
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 8.79$, df = 3 ($P = 0.03$); $I^2 = 66\%$								



(B)

Study or Subgroup	GLP–1 RA plus SGLT2i Mean	SD	Total	SGLT2i Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Simultaneous initiation of GLP–1 RA plus SGLT2i								
Ali 2020[36]	−1.67	1.12	15	−0.89	0.93	15	11.0%	−0.78 [−1.52; −0.04]
Ikonomidis 2018[28]	−1.50	3.58	20	−0.80	2.24	20	2.9%	−0.70 [−2.55; 1.15]
Jabbour 2018[21]	−1.70	1.66	228	−1.06	1.82	230	19.5%	−0.64 [−0.96; −0.32]
Total (95% CI)			**263**			**265**	**33.4%**	**−0.66 [−0.95; −0.37]**
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.12$, df = 2 ($P = 0.94$); $I^2 = 0\%$								
Sequential addition of GLP–1 RA to SGLT2i								
Blonde 2020[33]	−1.00	0.86	195	−0.32	0.83	95	21.8%	−0.68 [−0.89; −0.47]
Ludvik 2018[34]	−1.27	0.74	266	−0.54	0.74	133	22.6%	−0.73 [−0.88; −0.58]
Zinman 2019[35]	−1.50	0.74	151	−0.10	0.86	151	22.2%	−1.40 [−1.58; −1.22]
Total (95% CI)			**612**			**379**	**66.6%**	**−0.94 [−1.39; −0.49]**
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 38.05$, df = 2 ($P < 0.01$); $I^2 = 95\%$								
Total (95% CI)			**875**			**644**	**100.0%**	**−0.85 [−1.19; −0.52]**
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 41.09$, df = 5 ($P < 0.01$); $I^2 = 88\%$								



Diabetes Obes Metab. 2020;22(10):1857-1868

AGENDA

- Razionale fisiopatologico e clinico dell'associazione
- Effetti dell'associazione sul compenso glicemico
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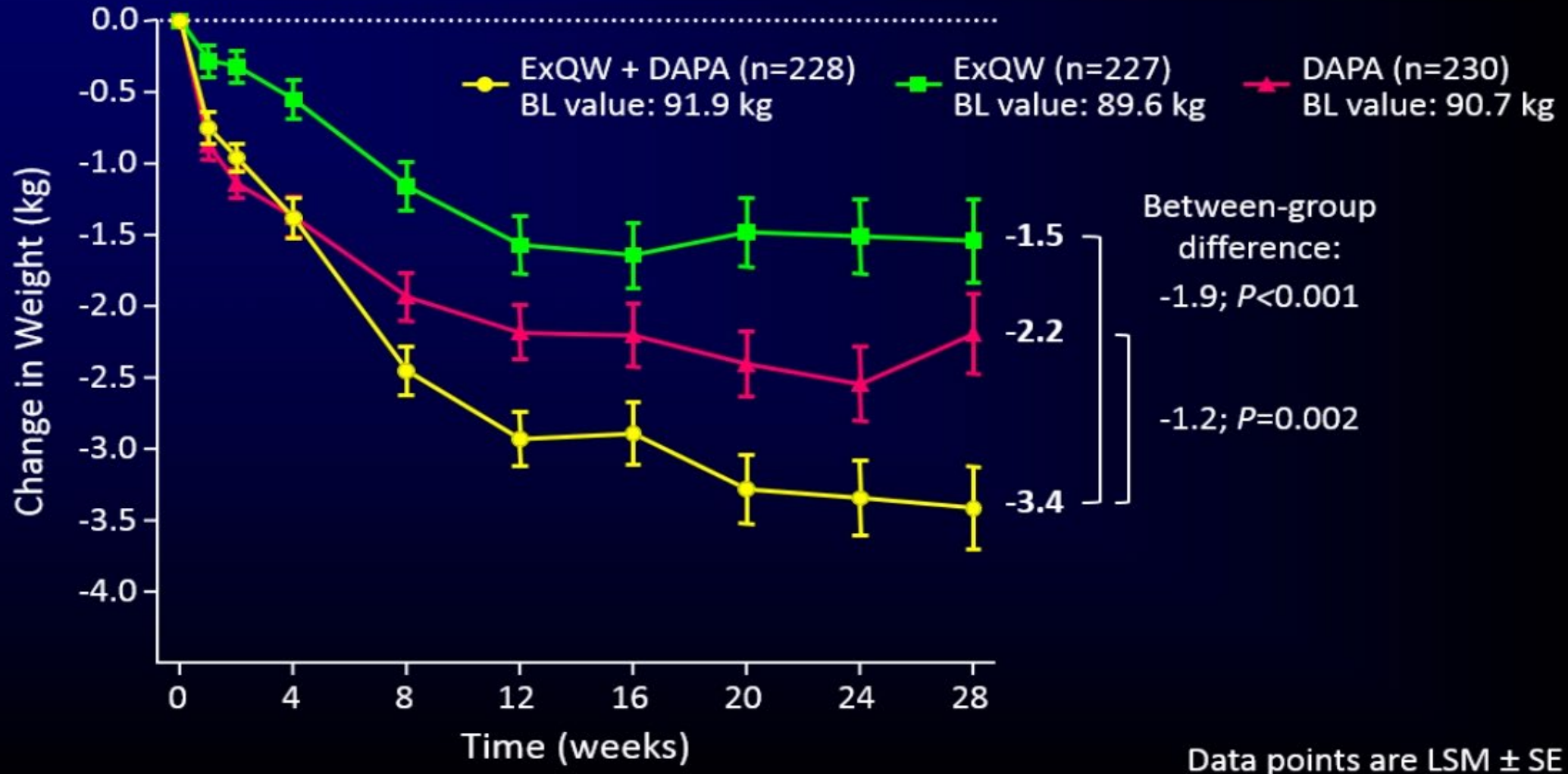
- Effetti dell'associazione sugli eventi
- Possibili argomenti a sfavore

Change in Weight



Data points are LSM ± SE

PESO

Change from baseline in body weight (kg)

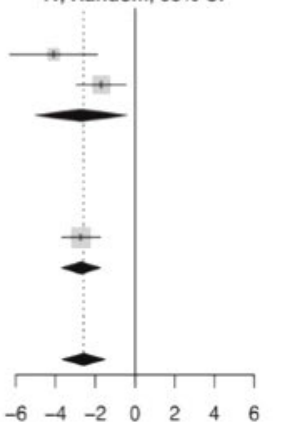
GLP-1 RA plus SGLT2i compared with:

(A) GLP-1RA

(B) SGLT2i

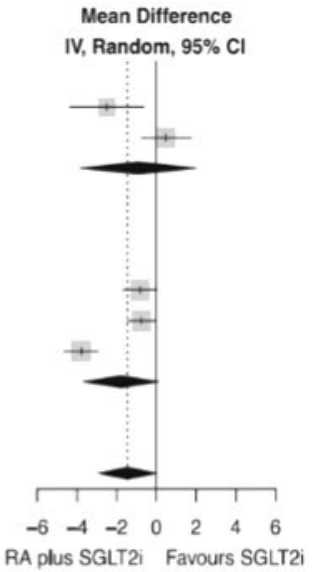
(A)

Study or Subgroup	GLP-1 RA plus SGLT2i Mean	SD	Total	GLP-1 RA Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Simultaneous initiation of GLP-1 RA plus SGLT2i								
Ali 2020[36]	−6.00	3.10	15	−1.90	3.10	15	17.9%	−4.10 [−6.32; −1.88]
Jabbour 2018[21]	−2.50	6.04	228	−0.80	7.53	227	36.6%	−1.70 [−2.95; −0.45]
Total (95% CI)			**243**			**242**	**54.6%**	**−2.72 [−5.04; −0.39]**
Heterogeneity: $Tau^2 = 2.03$; $Chi^2 = 3.41$, df = 1 ($P = 0.06$); $I^2 = 71\%$								
Sequential addition of SGLT2i to GLP-1 RA								
Fulcher 2016[24]	−3.32	2.30	64	−0.60	2.19	29	45.4%	−2.72 [−3.70; −1.74]
Total (95% CI)			**64**			**29**	**45.4%**	**−2.72 [−3.70; −1.74]**
Heterogeneity: not applicable								
Total (95% CI)			**307**			**271**	**100.0%**	**−2.59 [−3.68; −1.51]**
Heterogeneity: $Tau^2 = 0.43$; $Chi^2 = 3.75$, df = 2 ($P = 0.15$); $I^2 = 47\%$								



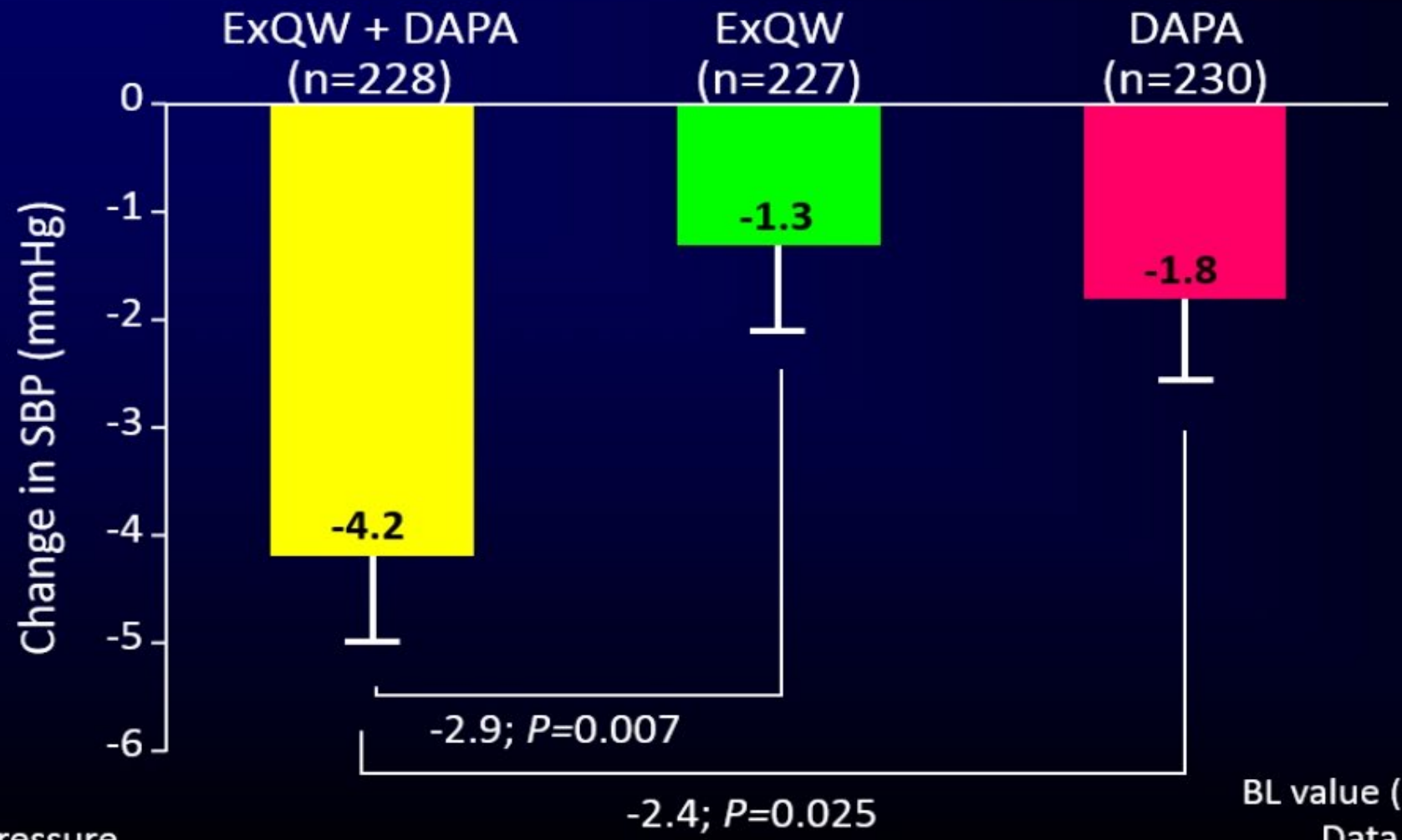
(B)

Study or Subgroup	GLP-1 RA plus SGLT2i Mean	SD	Total	SGLT2i Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Simultaneous initiation of GLP-1 RA plus SGLT2i								
Ali 2020[36]	−6.00	3.10	15	−3.50	1.94	15	16.8%	−2.50 [−4.35; −0.65]
Jabbour 2018[21]	−2.50	6.04	228	−3.00	7.58	230	19.5%	0.50 [−0.75; 1.75]
Total (95% CI)			**243**			**245**	**36.3%**	**−0.92 [−3.86; 2.02]**
Heterogeneity: $Tau^2 = 3.85$; $Chi^2 = 6.92$, df = 1 ($P < 0.01$); $I^2 = 86\%$								
Sequential addition of GLP-1 RA to SGLT2i								
Blonde 2020[33]	−2.84	3.83	196	−2.02	3.32	97	21.1%	−0.82 [−1.67; 0.03]
Ludvik 2018[34]	−2.85	3.50	271	−2.10	3.51	137	21.5%	−0.75 [−1.47; −0.03]
Zinman 2019[35]	−4.70	3.93	151	−0.90	3.81	151	21.0%	−3.80 [−4.67; −2.93]
Total (95% CI)			**618**			**385**	**63.7%**	**−1.78 [−3.69; 0.12]**
Heterogeneity: $Tau^2 = 2.66$; $Chi^2 = 32.94$, df = 2 ($P < 0.01$); $I^2 = 94\%$								
Total (95% CI)			**861**			**630**	**100.0%**	**−1.46 [−2.94; 0.03]**
Heterogeneity: $Tau^2 = 2.52$; $Chi^2 = 44.08$, df = 4 ($P < 0.01$); $I^2 = 91\%$								



Diabetes Obes Metab. 2020;22(10):1857-1868

Change in Systolic Blood Pressure



SBP, systolic blood pressure.

BL value (SD): 130 (13) mmHg
Data values are LSM ± SE

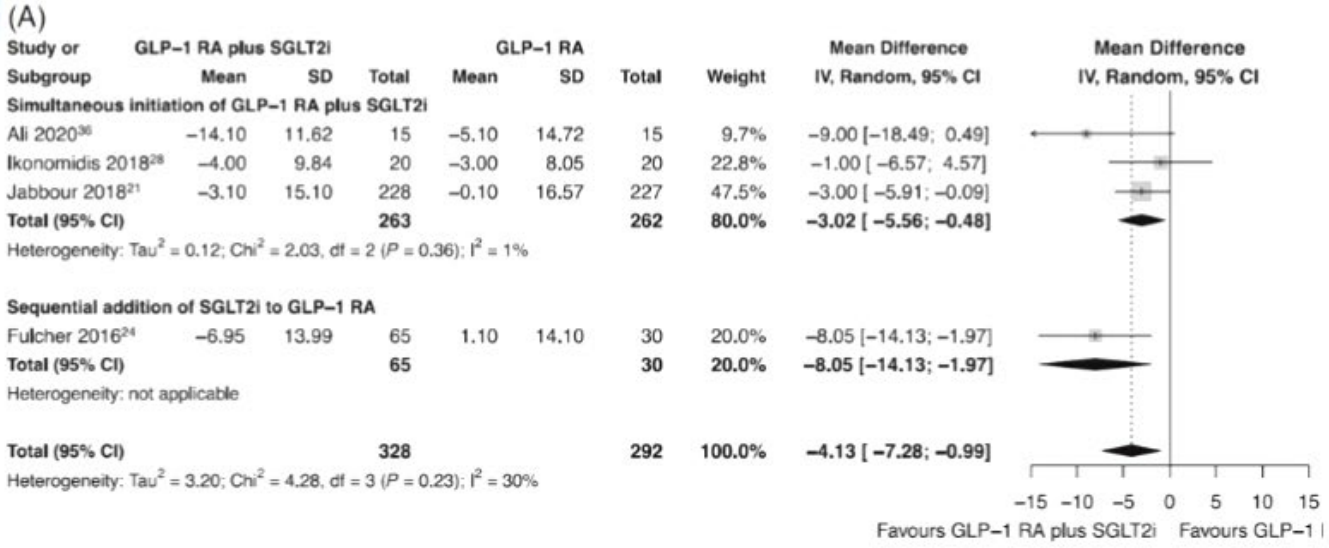
PRESSIONE ARTERIOSA

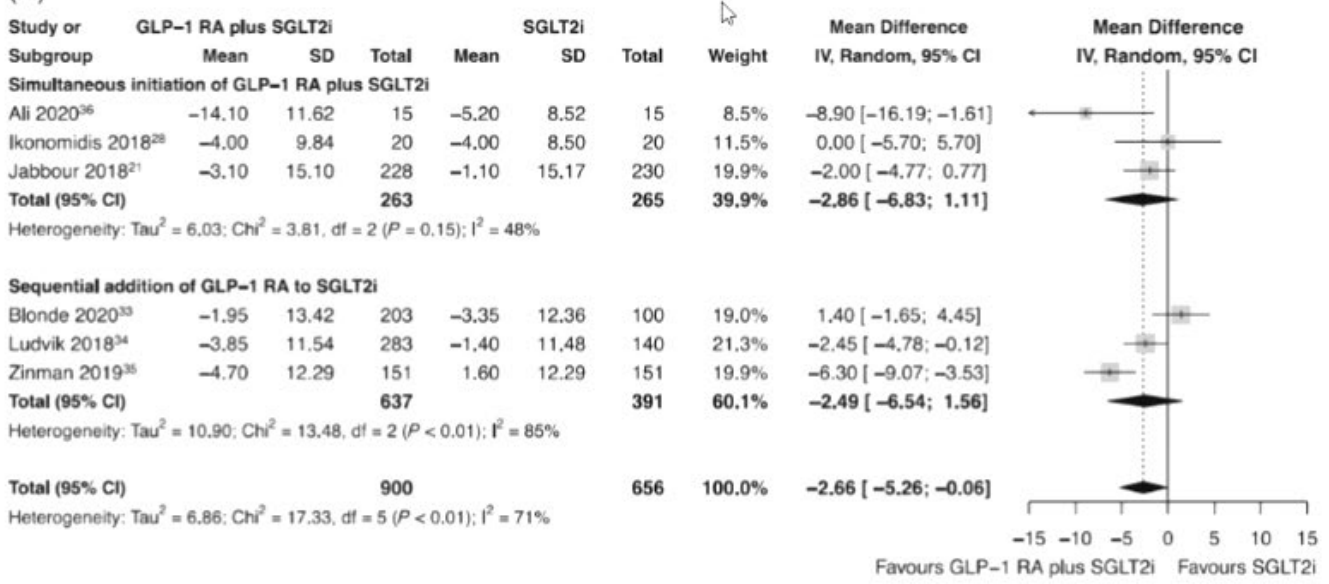
Change from baseline in systolic BP (mmHg)

GLP-1 RA plus SGLT2i compared with:

(A) GLP-1RA

(B) SGLT2i



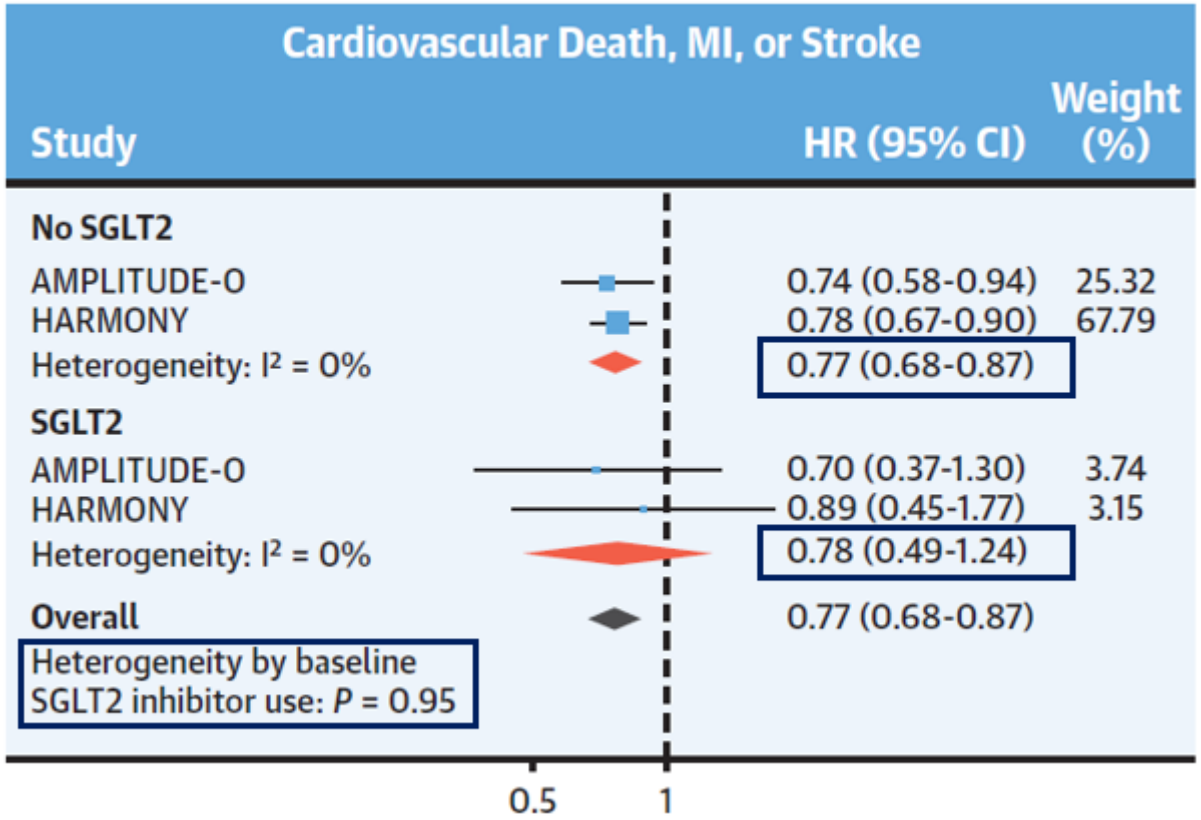


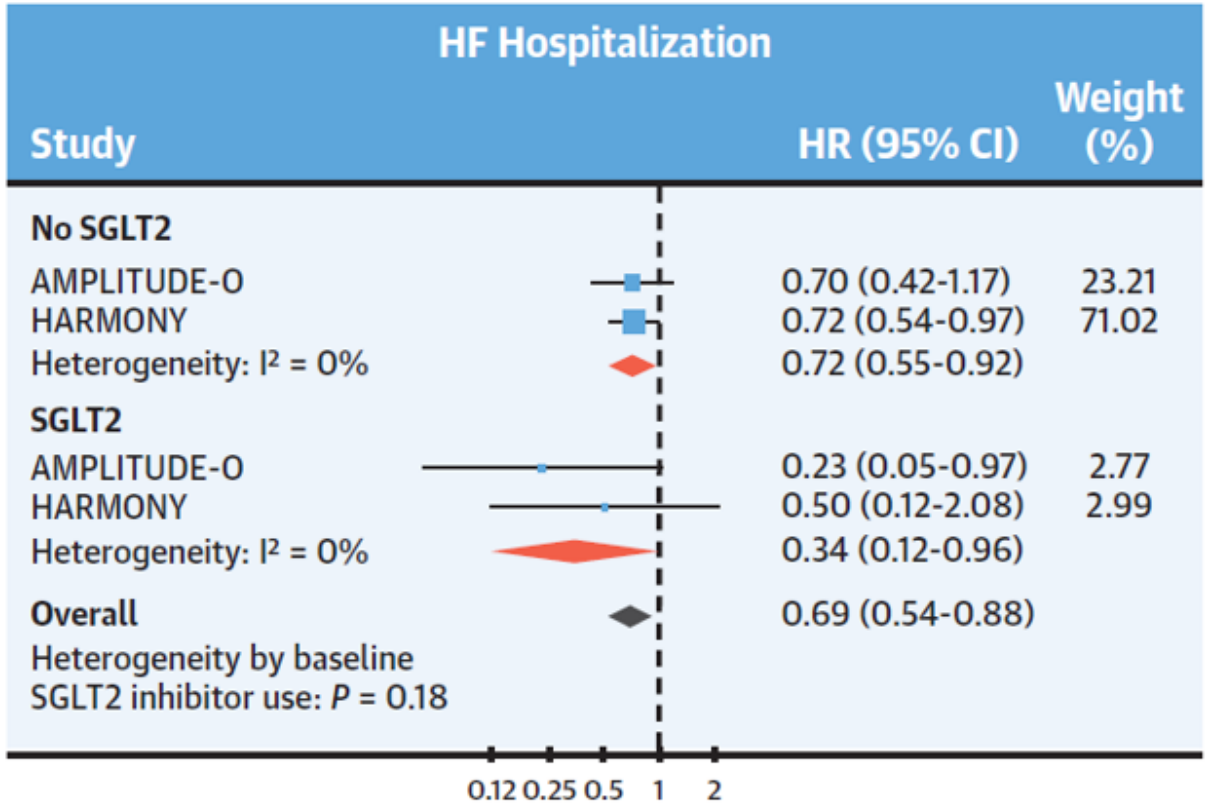
Diabetes Obes Metab. 2020;22(10):1857-1868

AGENDA

- Razionale fisiopatologico e clinico dell'associazione
- Effetti dell'associazione sul compenso glicemico
- Effetti dell'associazione sui fattori di rischio cardiovascolare
- **Effetti dell'associazione sugli eventi**
- Possibili argomenti a sfavore

DATI DA RCT





Neves JS, et al. J Am Coll Cardiol. 2023;82(6):517-525.

DATI DA RCT

PREvention of Cardlovascular and DiabEtic kidNey Disease in Type 2 Diabetes (PRECIDENTD)

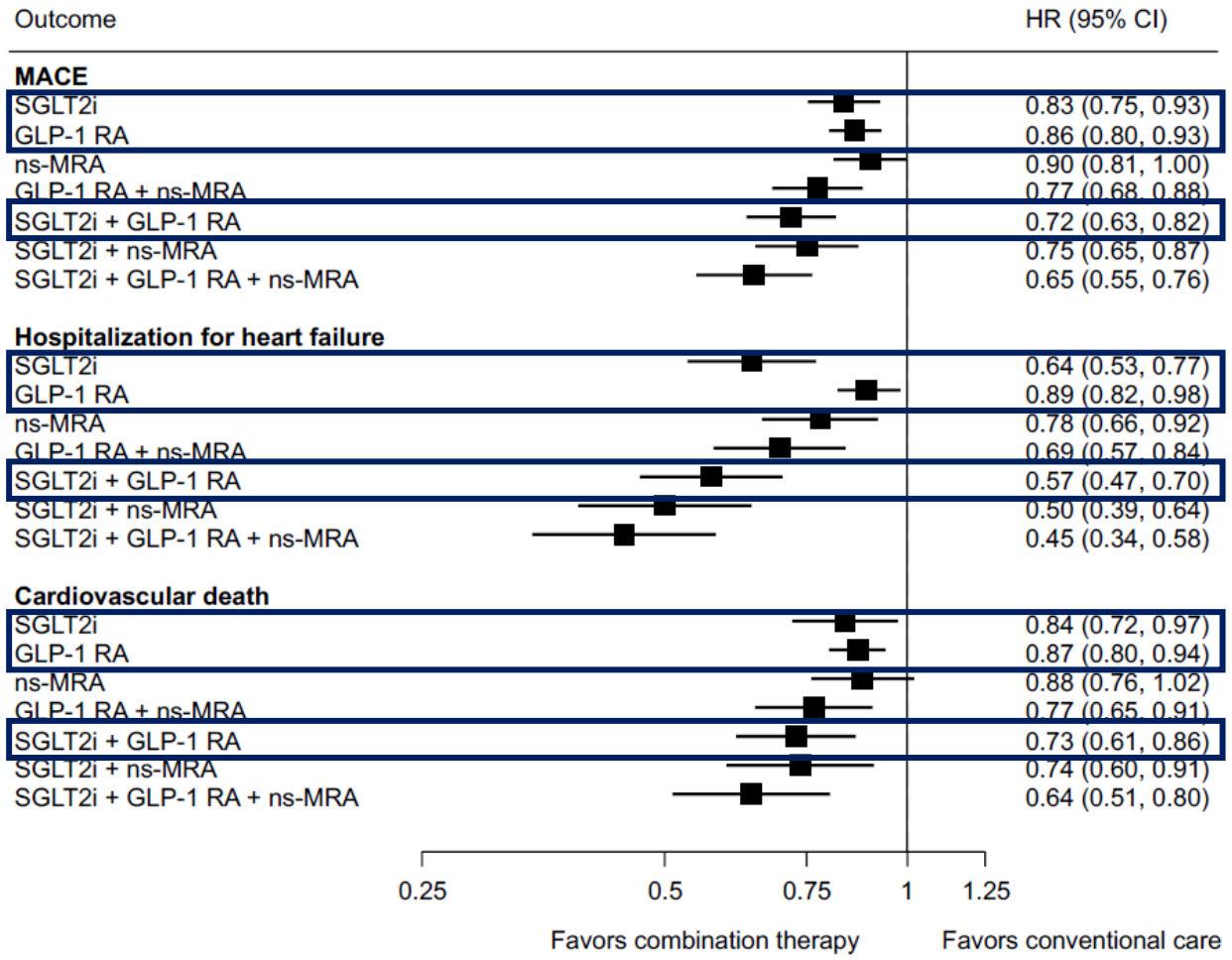
- **Sponsor**: Brigham and Women Hospital
- **Design:** Randomized, open label, pragmatic clinical trial
- **9000** patients with T2D and either established (>70%) or at high risk for ASCVD.
- **3 study arms**:
  - GLP1-RA: dulaglutide/semaglutide/liraglutide
  - SGLT2-i: empagliflozin/dapagliflozin/canagliflozin
  - GLP1-RA + SGLT2-i
- **Primary endpoint**:
  - Myocardial infarction
  - Stroke
  - Arterial revascularization
  - Hospitalization for heart failure
  - End-stage kidney disease
  - Kidney transplantation
  - Mortality
- **Estimated completion**: April 30, 2028

ClinicalTrials.gov Identifier: NCT05390892

MODELLI PREDITTIVI

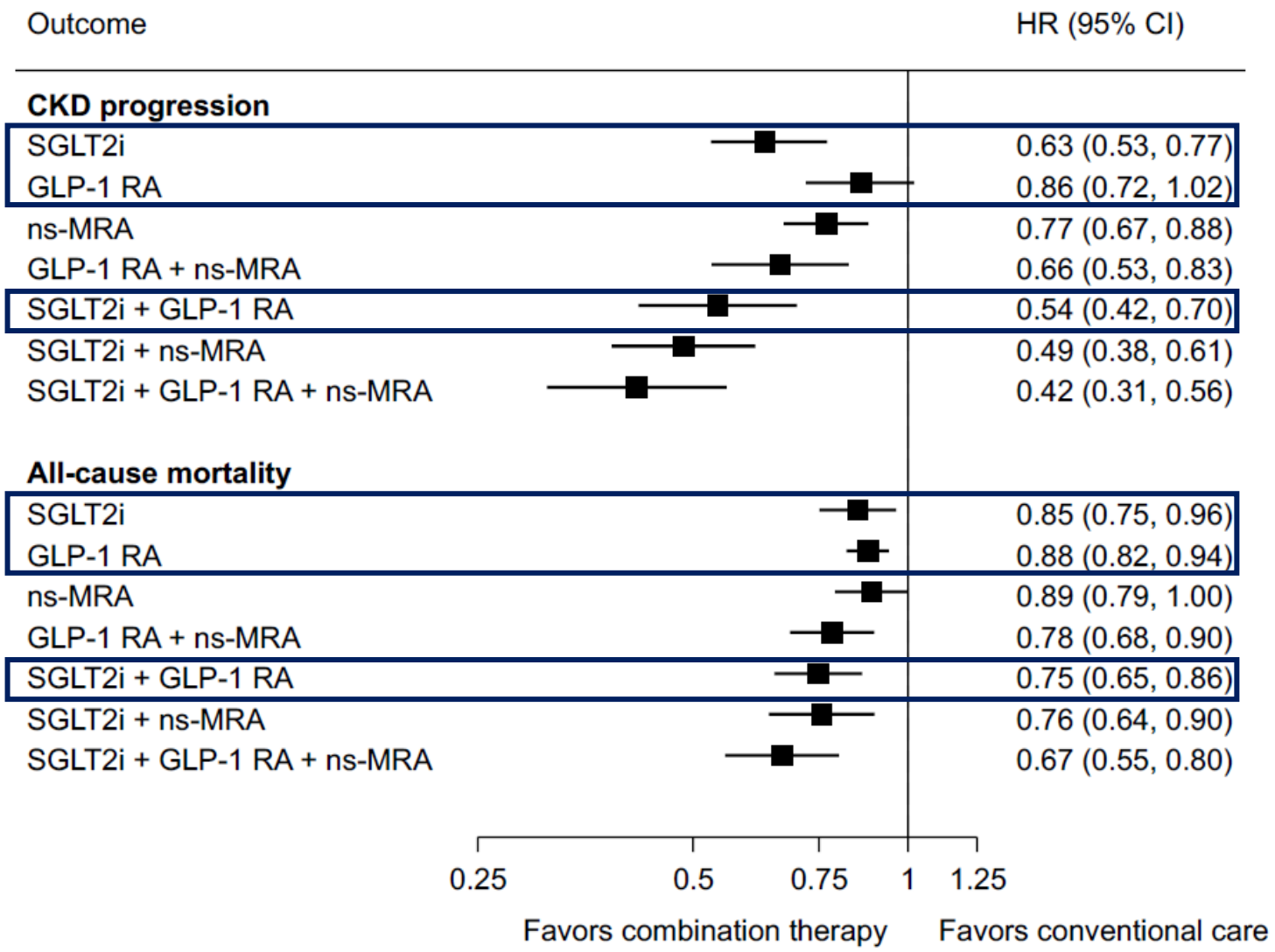
Modello statistico basato su dati da RCTs effettuati con GPL1-RA, SGLT2-I e MRAs

- Ipotizzato paziente di 50 anni con microalbuminuria
- Lifetime follow-up



Neuen et al. Circulation 2023

MODELLI PREDITTIVI



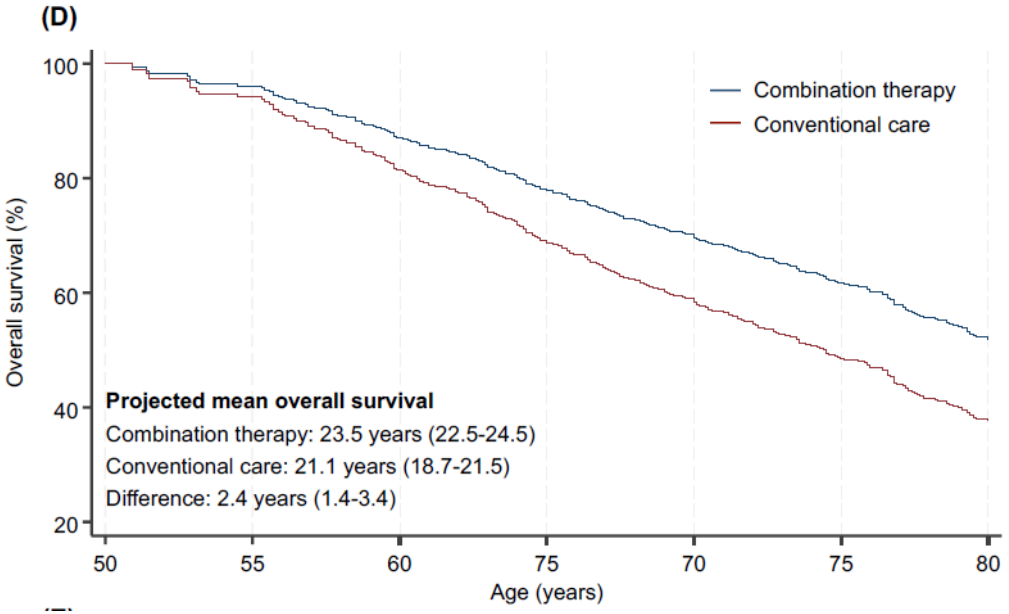
Neuen et al. Circulation 2023

EVENTI

Un **50enne** che inizia la terapia di combinazione **guadagna**:

- MACE-free survival: 3.2 anni, IC 95% 2,1-4,3.
- HF-free survival: 3.2 anni, IC 95% 2,4-4,0)
- CKD-free survival: 5.5 anni, IC 95% 4,0-6,7),
- Survival from cardiovascular death: 2.2 anni, IC 95% 1,2-3,0
- **<u>Overall survival: 2.4 anni, IC 95% 1,4-3,4</u>**

Guadagni attenuati ma clinicamente rilevanti sono stati osservati in analisi che assumevano effetti additivi del 50%.



Neuen et al. Circulation 2023

AGENDA

- Razionale fisiopatologico dell'associazione
- Effetti protettivi di ciascuna classe
- Effetti dell'associazione sul compenso glicemico
- Effetti dell'associazione sui fattori di rischio cardiovascolare
- Effetti dell'associazione sugli eventi
- **Possibili argomenti a sfavore**

ARGOMENTI A SFAVORE

- Effetti collaterali
- Costi

Adverse Events

	ExQW + DAPA (n=228)	ExQW (n=227)	DAPA (n=230)
Any AE	131 (56.7)	124 (53.9)	121 (51.9)
Any SAE	10 (4.3)	8 (3.5)	10 (4.3)
Deaths	3 (1.3)	1 (0.4)	1 (0.4)
AE discontinuations	9 (3.9)	11 (4.8)	5 (2.1)
AEs occurring in ≥5% of patients			
Injection-site nodule	18 (7.8)	14 (6.1)	12 (5.2)
Nausea	12 (5.2)	17 (7.4)	7 (3.0)
Diarrhoea	10 (4.3)	13 (5.7)	7 (3.0)
Urinary tract infection	10 (4.3)	12 (5.2)	13 (5.6)

All values are number (proportion of patients). AE, adverse event; SAE, serious adverse event.

Adverse Events of Special Interest

	ExQW + DAPA (n=228)	ExQW (n=227)	DAPA (n=230)
Potentially volume depletion related	2 (0.9)	0 (0.0)	3 (1.3)
Acute renal disorders	0 (0.0)	2 (0.9)	1 (0.4)
Pancreatitis	1 (0.4)	1 (0.4)	0 (0.0)
Diabetic ketoacidosis	0 (0.0)	1 (0.4)	0 (0.0)
Events suggestive of genital infections	10 (4.3)	4 (1.7)	13 (5.6)
Hypoglycaemia			
Major[a]/Minor[b]	0/0	0/0	0/0
Other	8 (3.5)	3 (1.3)	3 (1.3)

[a]Loss of consciousness, seizure, or coma resolving after glucose/glucagon OR severe impairment requiring assistance and glucose <3 mmol/L (<54 mg/dL); [b]Non-major hypoglycaemia symptoms and glucose <3 mmol/L (<54 mg/dL).

ARGOMENTI A SFAVORE

Severe hypoglycemia

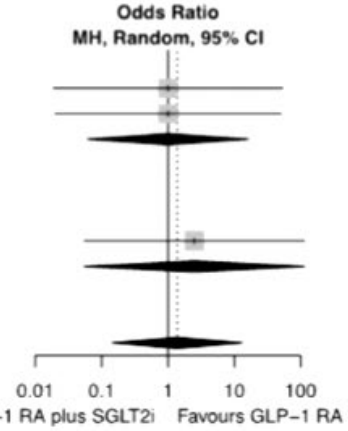
GLP-1 RA plus SGLT2i compared with:

(A) GLP-1RA

(B) SGLT2i

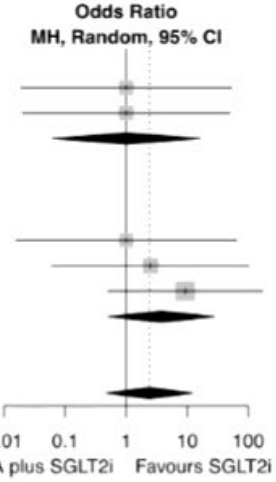
A

Study or Subgroup	GLP-1 RA plus SGLT2i Events	Total	GLP-1 RA Events	Total	Weight	Odds Ratio MH, Random, 95% CI
Simultaneous initiation of GLP-1 RA plus SGLT2i						
Ali 2020	0	15	0	15	32.1%	1.00 [0.02; 53.66]
Jabbour 2018	0	231	0	230	33.1%	1.00 [0.02; 50.61]
Total (95% CI)		**246**		**245**	**65.2%**	**1.00 [0.06; 16.37]**
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0$, df = 1 (P = 1.00); $I^2 = 0\%$						
Sequential addition of SGLT2i to GLP-1 RA						
Fulcher 2016	1	65	0	30	34.8%	2.50 [0.05; 114.58]
Total (95% CI)		**65**		**30**	**34.8%**	**2.50 [0.05; 114.58]**
Heterogeneity: not applicable						
Total (95% CI)		**311**		**275**	**100.0%**	**1.38 [0.14; 13.14]**
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.15$, df = 2 (P = 0.93); $I^2 = 0\%$						



B

Study or Subgroup	GLP-1 RA plus SGLT2i Events	Total	SGLT2i Events	Total	Weight	Odds Ratio MH, Random, 95% CI
Simultaneous initiation of GLP-1 RA plus SGLT2i						
Ali 2020	0	15	0	15	16.9%	1.00 [0.02; 53.66]
Jabbour 2018	0	231	0	233	17.4%	1.00 [0.02; 50.61]
Total (95% CI)		**246**		**248**	**34.2%**	**1.00 [0.06; 16.37]**
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0$, df = 1 (P = 1.00); $I^2 = 0\%$						
Sequential addition of GLP-1 RA to SGLT2i						
Blonde 2020	0	202	0	100	15.4%	1.00 [0.02; 64.81]
Ludvik 2018	1	283	0	140	19.2%	2.50 [0.06; 104.85]
Zinman 2019	4	150	0	151	31.2%	9.27 [0.50; 173.02]
Total (95% CI)		**635**		**391**	**65.8%**	**3.76 [0.50; 28.26]**
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.82$, df = 2 (P = 0.66); $I^2 = 0\%$						
Total (95% CI)		**881**		**639**	**100.0%**	**2.39 [0.47; 12.27]**
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 1.44$, df = 4 (P = 0.84); $I^2 = 0\%$						



Diabetes Obes Metab. 2020;22(10):1857-1868

COSTI

- The issue of cost-effectiveness is particularly relevant for high cost of GLP-1 RA, such as semaglutide or tirzepatide

- In the US, the costs of GLP-1 RA and SGLT2i would need to fall by at least 70% to be cost-effective as first-line therapy
- In Australia, GLP-1 RA were unlikely to be cost-effective either for primary or secondary cardiovascular prevention, whereas SGLT2i were found to be cost-effective on both occasions
- GLP-1 RA were not cost-effective in 67 low-income or middle-income countries, unlike SGLT2i
- In high-income countries GLP-1 RA were not cost-effective compared to DPP-4 inhibitors, sulphonylureas or thiazolidinediones

Ann Intern Med 2022;175(10):1392–1400
Diabetologia 2023;66(4):642–656
Lancet Diabetes Endocrinol 2021; 9(12):825–836
BMJ Open Diab Res Care 2020;8:e001020

TAKE-HOME MESSAGES

SGLT2i & GLP-1 RA combination therapy could be used in patients with

- ASCVD or Indicators of high risk
- Heart Failure
- Chronic kidney disease
- Uncontrolled glycemia and body weight

BUT

Caution is warranted in older frail individuals

Cost (particularly) of GLP-1 RA would need to fall by >> to be cost-effective

Grazie dell’attenzione