SGLT2 inibitori + agonisti recettoriali del GLP-1

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Riccardo C. Bonadonna dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

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Stock/Shareholder: Nessuno

Consulente: Nessuno

Dipendente: Nessuno

Altro: Nessuno

SGLT2i + GLP1R-A: mappa mentale

- **Additività/sinergia/complementarietà nella farmacodinamica**
- **Additività/sinergia nei fenotipi intermedi clinici**
- **Additività/sinergia nella protezione d'organo**

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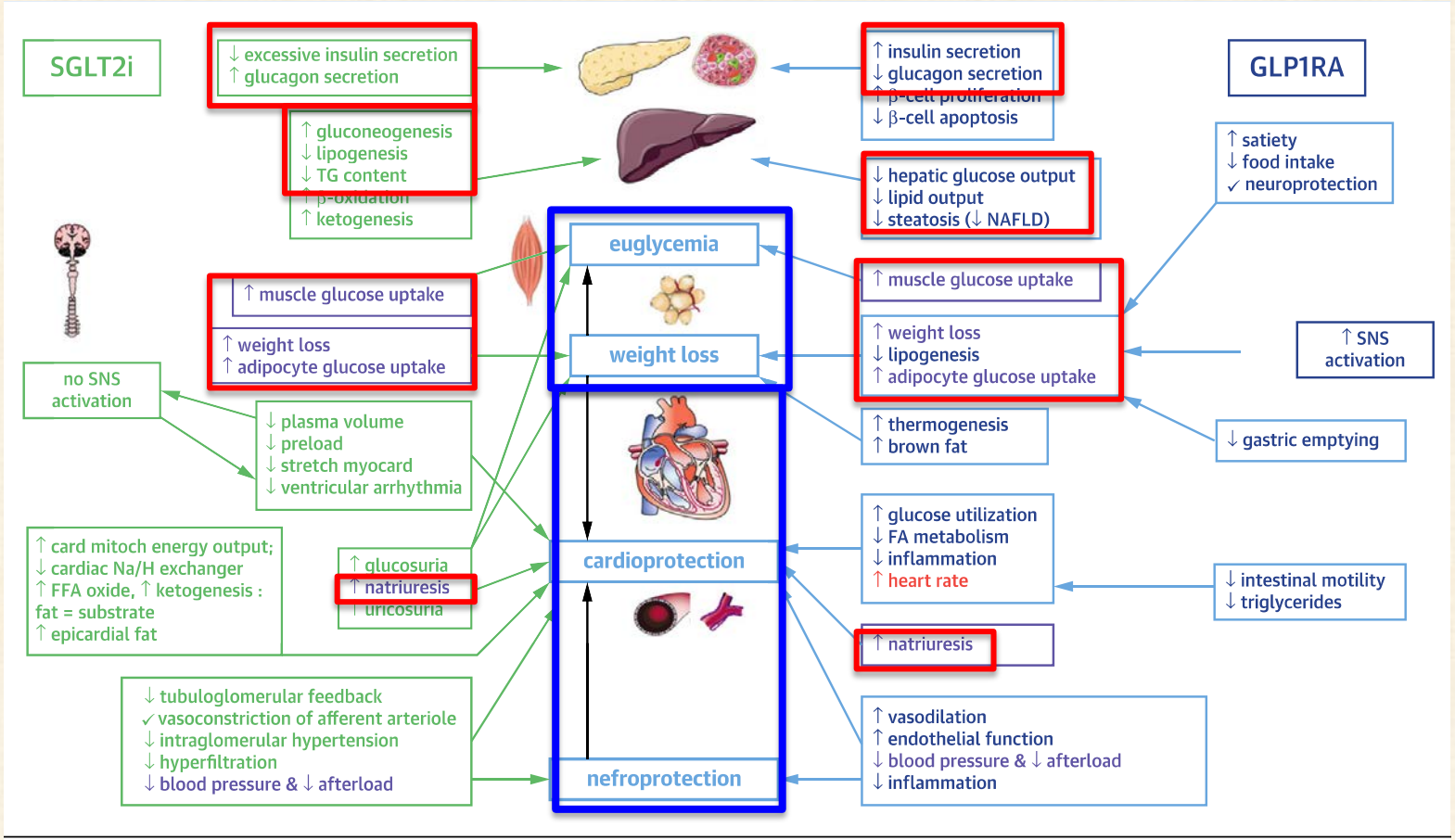
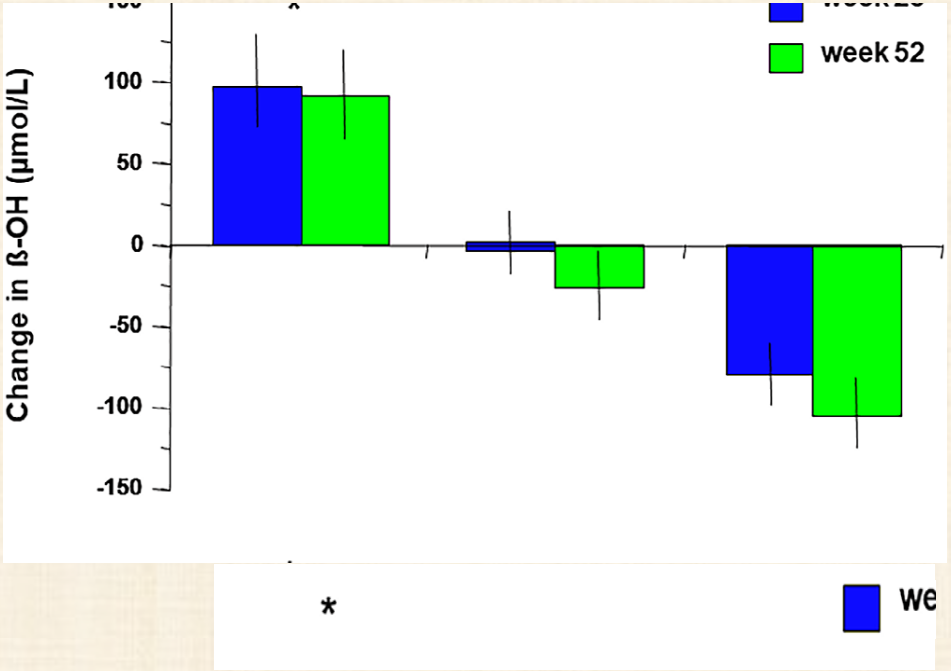
Physiologic mechanisms of SGLT2i and GLP1R-A in diabetes



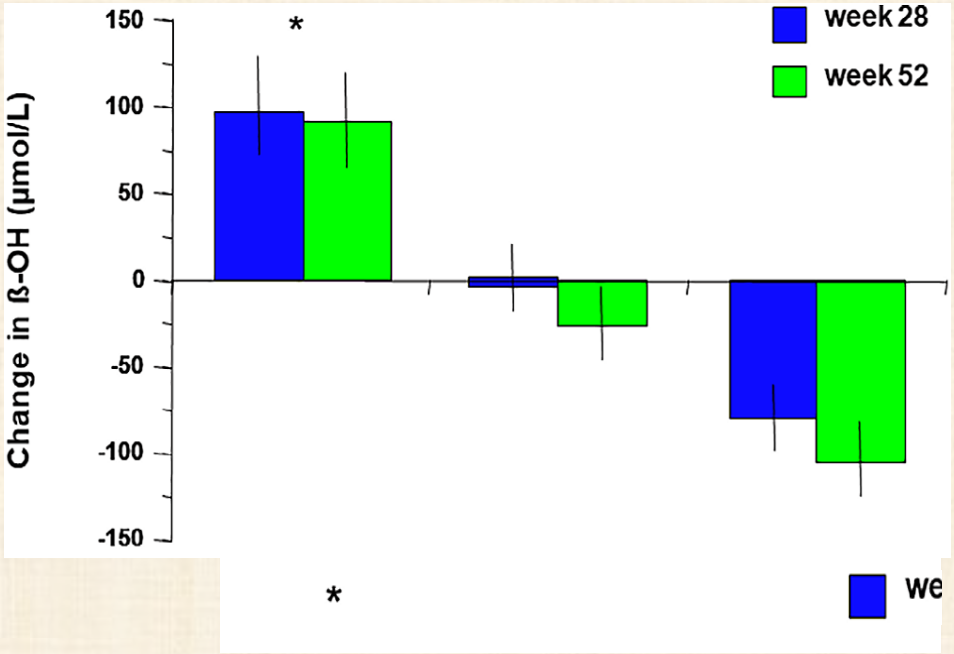
Wilcox T et al.; JACC 2020

Changes in plasma β-OH-butyrate and FFA from baseline in people with type 2 diabetes randomized to dapagliflozin or dapagliflozin+weekly exenatide or weekly exenatide

β-OH-butyrate



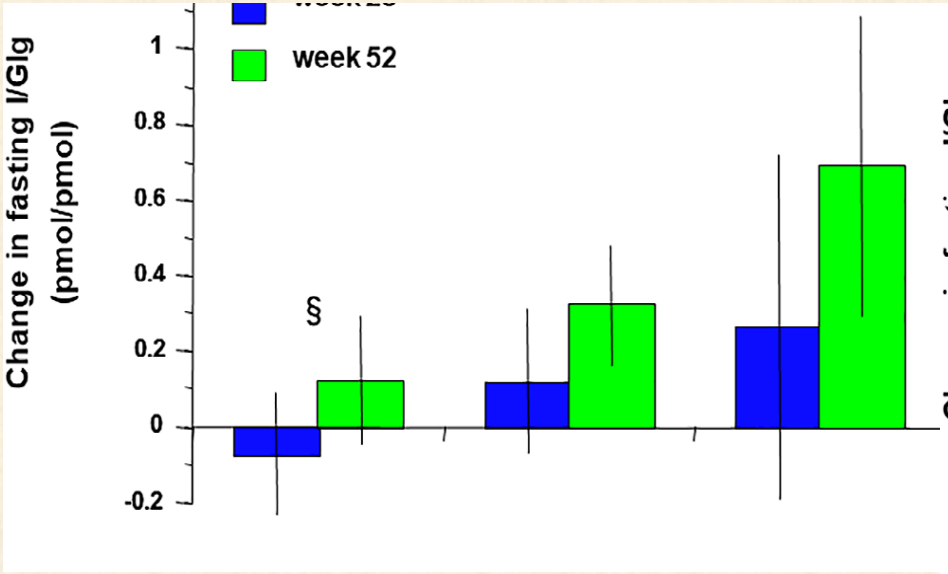
Free fatty acids



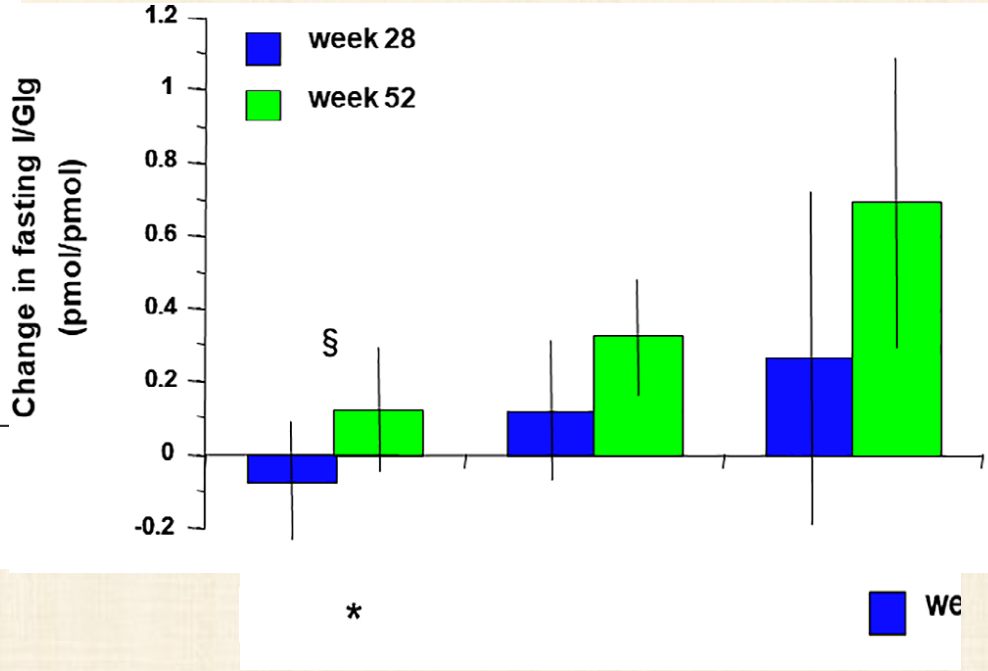
Ferrannini E et al.; Diab Obes & Metabol 2020

Changes in fasting and post-prandial insulin/glucagon ratio in people with type 2 diabetes randomized to dapagliflozin or dapagliflozin+weekly exenatide or weekly exenatide

Overnight fast



Postprandial



Ferrannini E et al.; Diab Obes & Metabol 2020

SGLT2i + GLP1R-A: mappa mentale

✔ **Additività/sinergia/complementarietà nella farmacodinamica**

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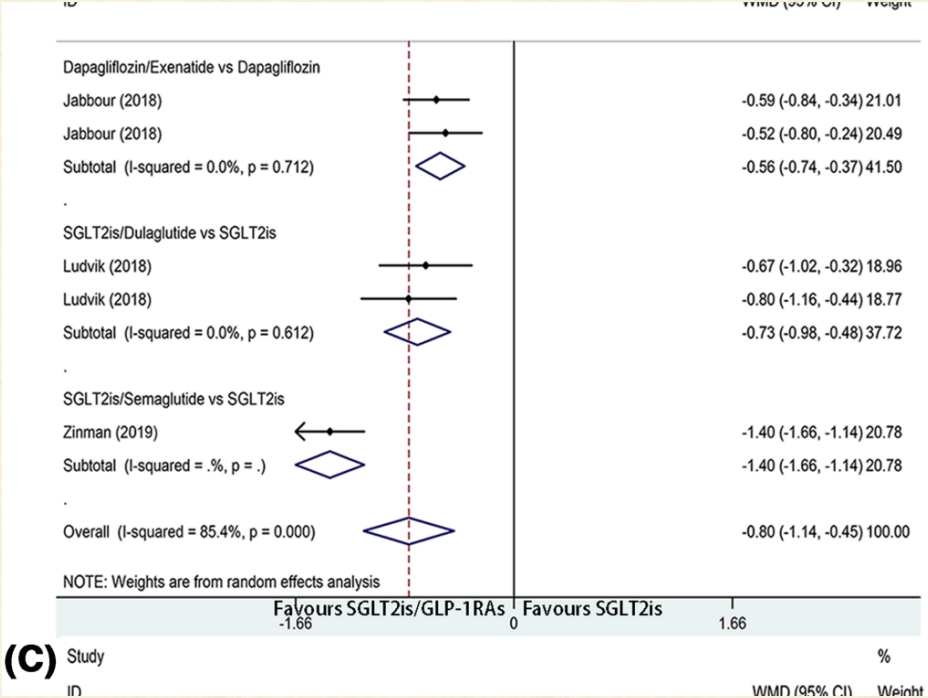
Summary of clinical studies of combination therapy with a SGLT2i and a GLP1R-A in patients with type 2 diabetes

Study (duration)	Design	No. of pts	Background therapy	Add-on therapy	Clinical outcomes[a]
DURATION-8 (52 weeks) [61]	R, DB	695	MET	ExQW + DAPA ExQW + PBO DAPA + PBO	↓ A1c, FPG, BW, and SBP No major hypoglycemia reported
AWARD-10 (24 weeks) [64]	R, DB	424	SGLT-2i ± MET	DULA 0.75 mg DULA 1.5 mg PBO	↓ A1c (both DULA doses) ↓ FPG, BW, and SBP (DULA 1.5 mg) 1 episode of severe hypoglycemia
Curtis et al. (48 weeks) [65]	Ret, Obs	14	GLP-1RA ± MET ± SU	SGLT-2i	↓ A1c and BW Most common AEs were UTI and polydipsia
Deol et al. (3–6 months) [67]	Ret, Obs	79	GLP-1RA ± MET ± INS	SGLT-2i	↓ A1c, BW, BMI, and INS dose
Harashima et al. (52 weeks) [63]	Non-R, PMS	71	LIRA	CANA	↓ A1c, FPG, BW, and SBP; ↑ HDL-C Mild hypoglycemia only
Saroka et al. (mean 10.7 months) [66]	Obs	75	GLP-1RA ± other GLTs	CANA	↓ A1c, BW, SBP, and DBP; ↑ HDL-C Drug-related AEs were yeast infections, UTI, dry mouth, diarrhea, and hypotension
Seino et al. (52 weeks) [62]	Non-R	76	LIRA	LUSEO	↓ A1c, FPG, BW, fat mass, and waist circumference Mild hypoglycemia only Most common AE was nasopharyngitis

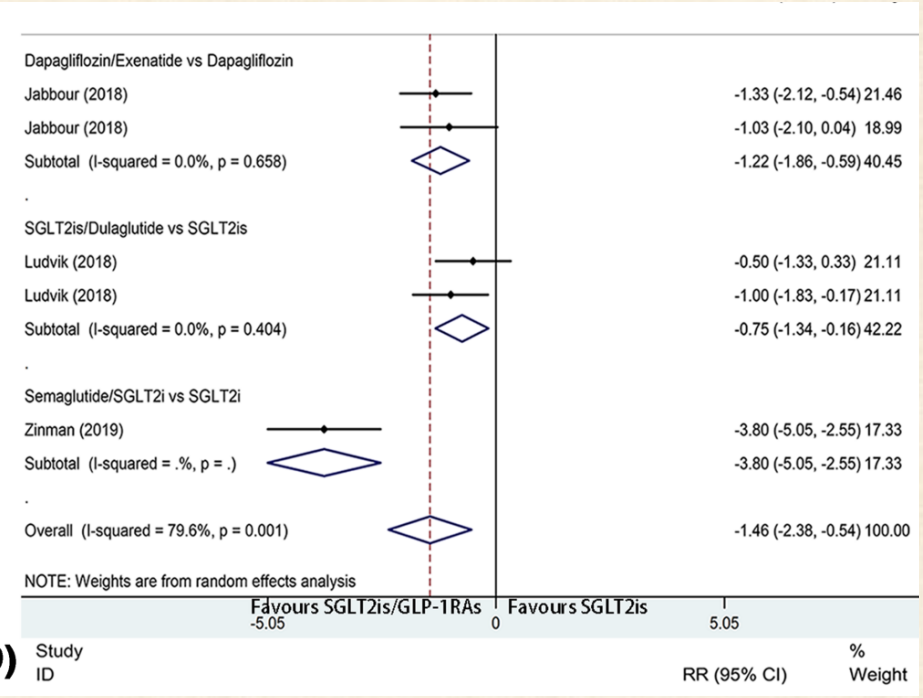
Lajara R; Postgraduate Medicine 2019

Forest plot of weighted mean difference of change in (left) HbA1c (%) and in (right) body weight (kg) in SGLT2i/GLP1R-A vs SGLT2i

HbA1c

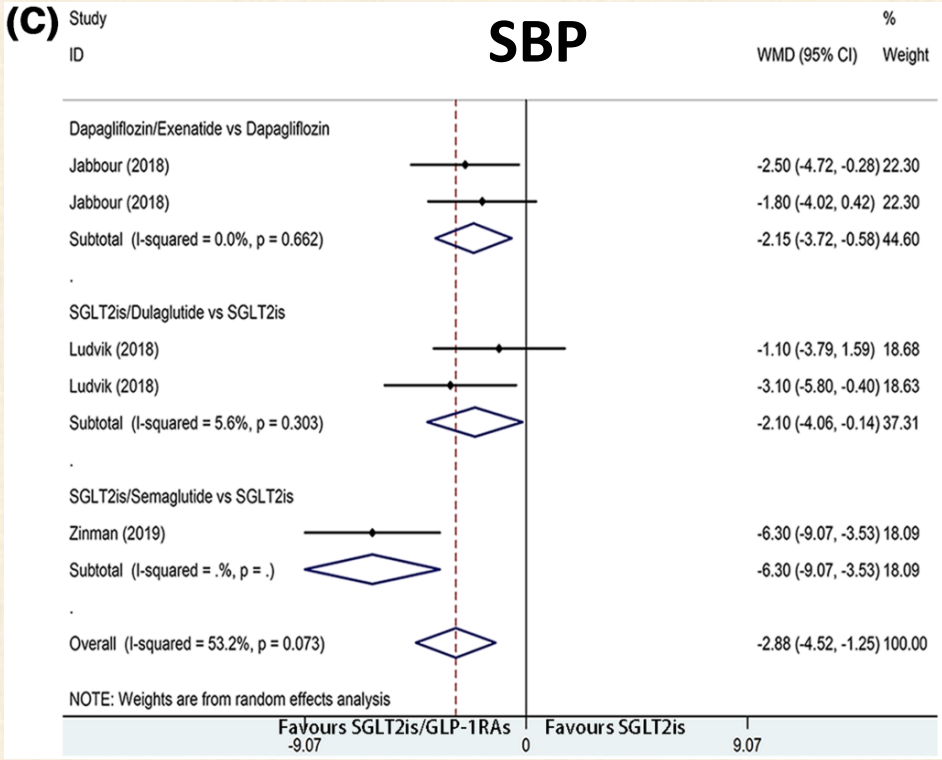


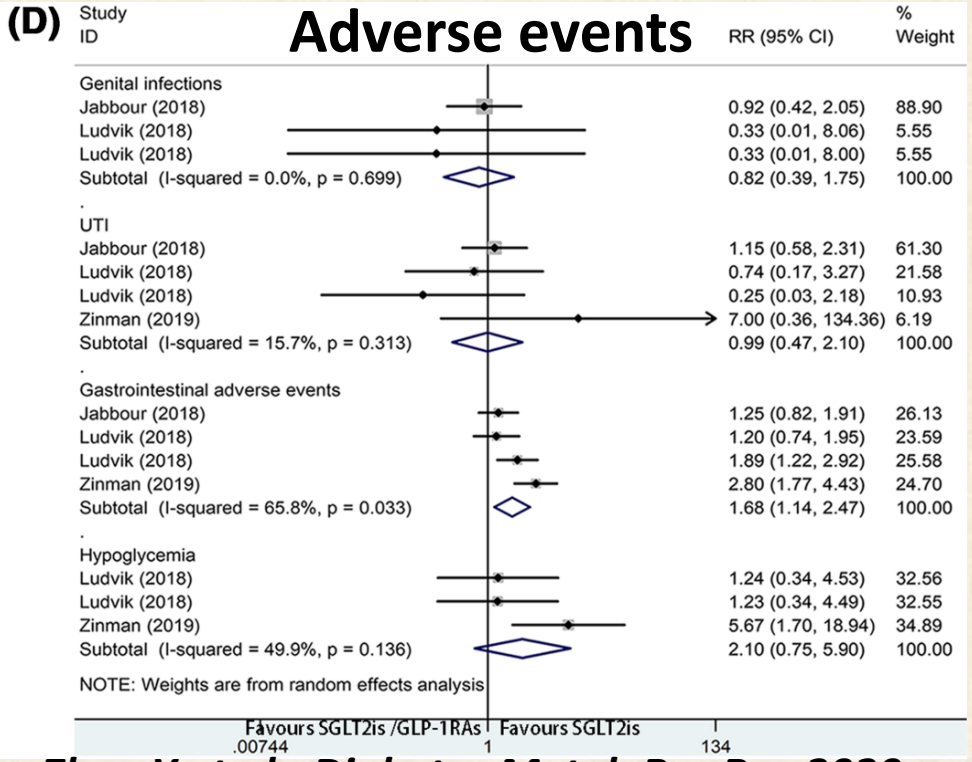
Body weight



Zhou Y et al.; Diabetes Metab Res Rev 2020

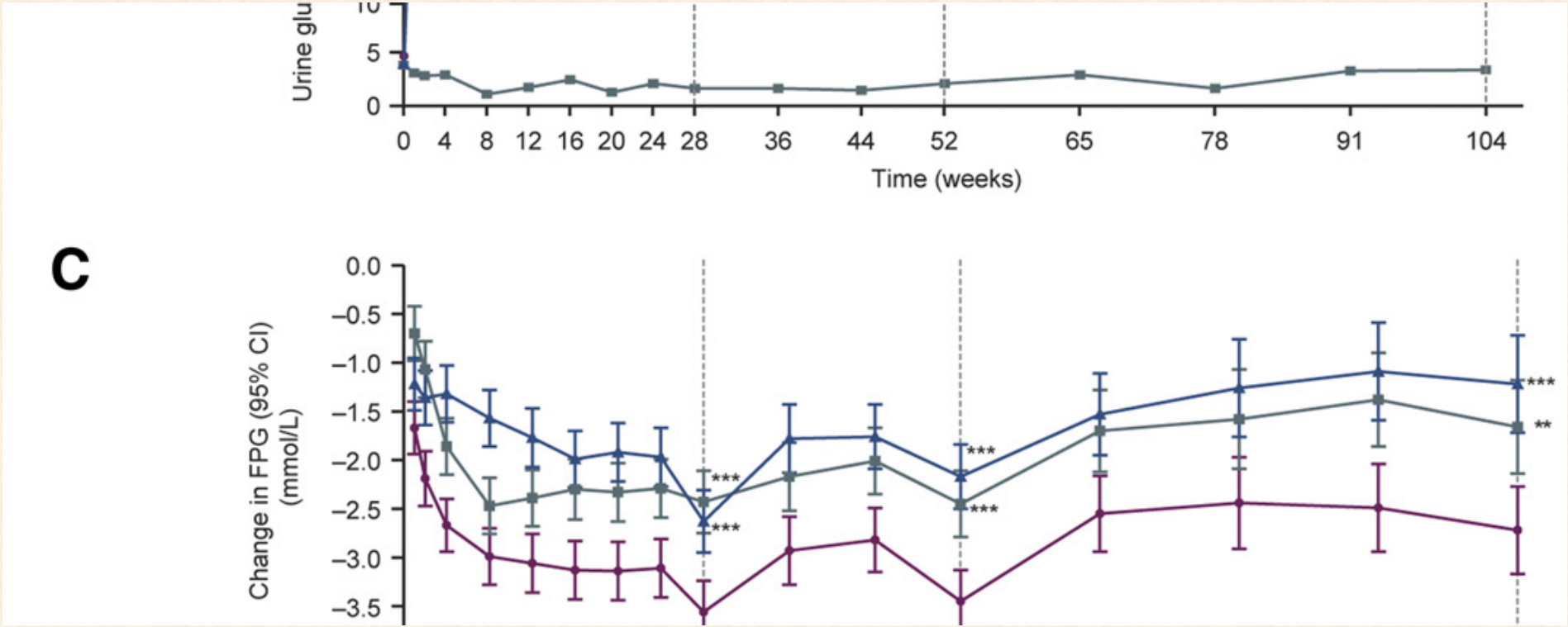
Forest plot of weighted mean difference in change of (left) systolic blood pressure (mm Hg) and of (right) relative risk of adverse events in SGLT2i/GLP1R-A vs SGLT2i





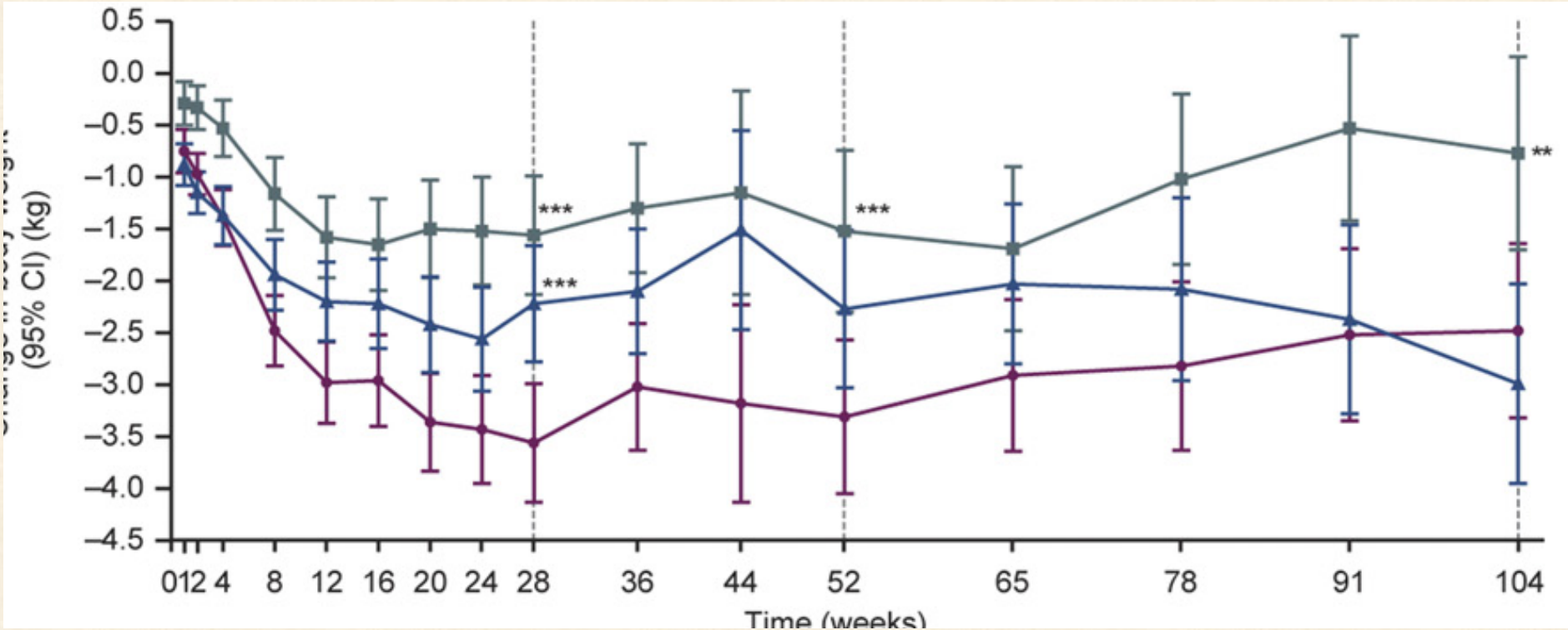
Zhou Y et al.; Diabetes Metab Res Rev 2020

DURATION-8 Study. Adjusted LSM changes of HbA1c in people with type 2 diabetes randomized to dapagliflozin (blue) or weekly exenatide (green) or dapagliflozin+weekly exenatide (purple) over 2 years



Jabbour SA et al.; Diabetes Care 2020

DURATION-8 Study. Adjusted LSM eGFR in people with type 2 diabetes randomized to dapagliflozin (blue) or weekly exenatide (green) or dapagliflozin+weekly exenatide (purple) over 2 years



Jabbour SA et al.; Diabetes Care 2020

SGLT2i + GLP1R-A: mappa mentale

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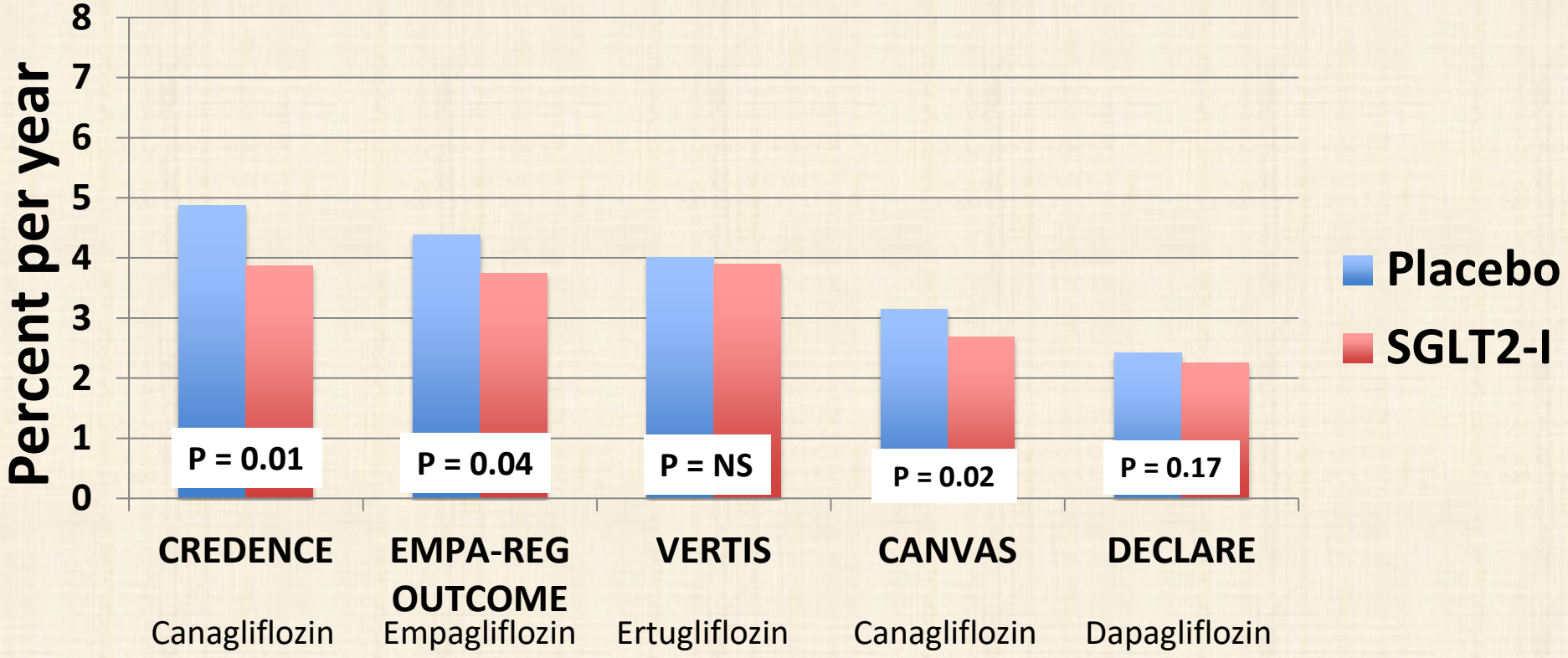
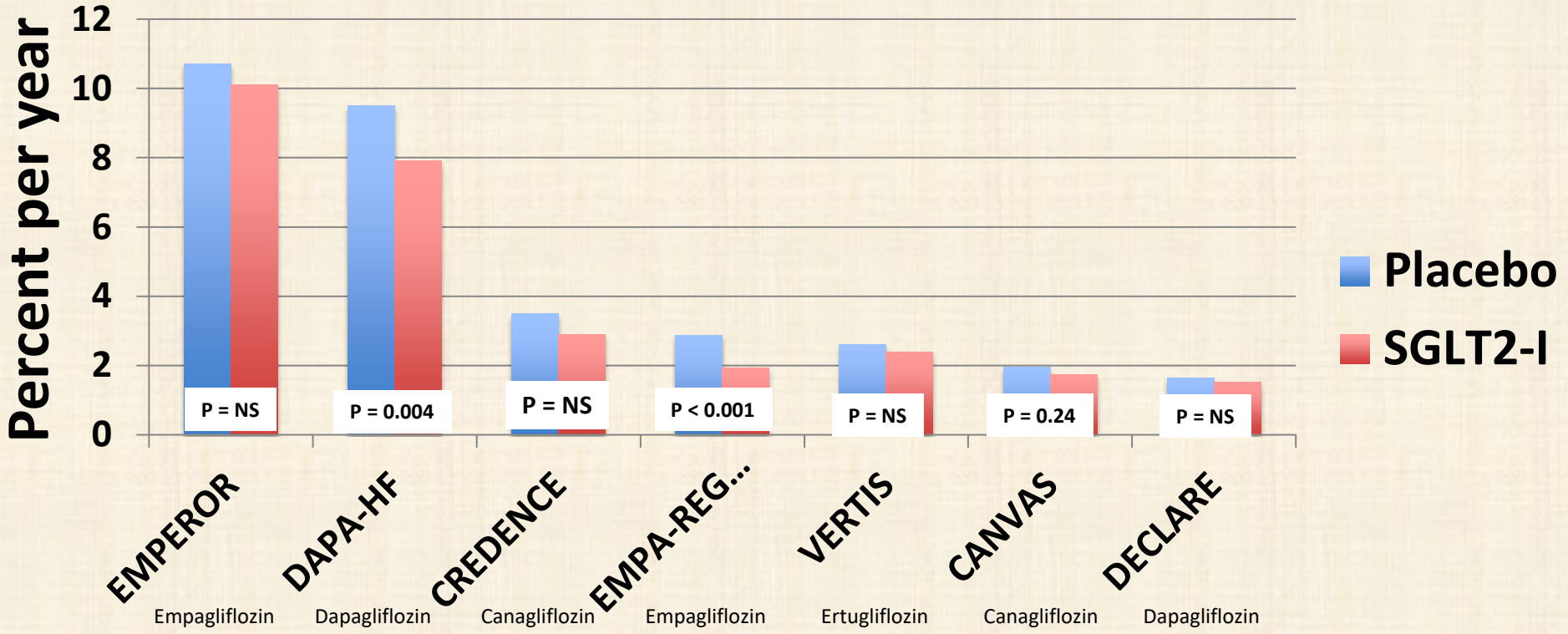
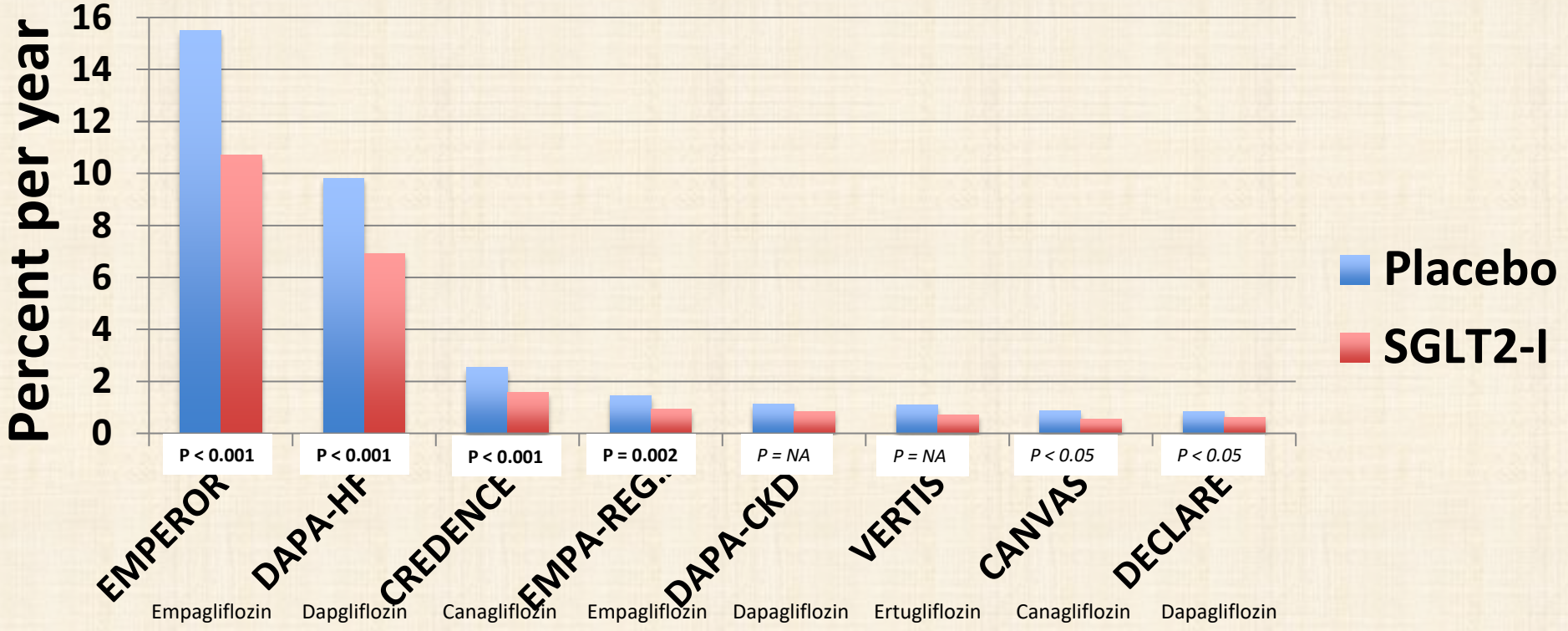
Incidence of MACE in the CVOTs with SGLT2-inhibitors



All cause death rate in the outcome trials with SGLT2-inhibitors

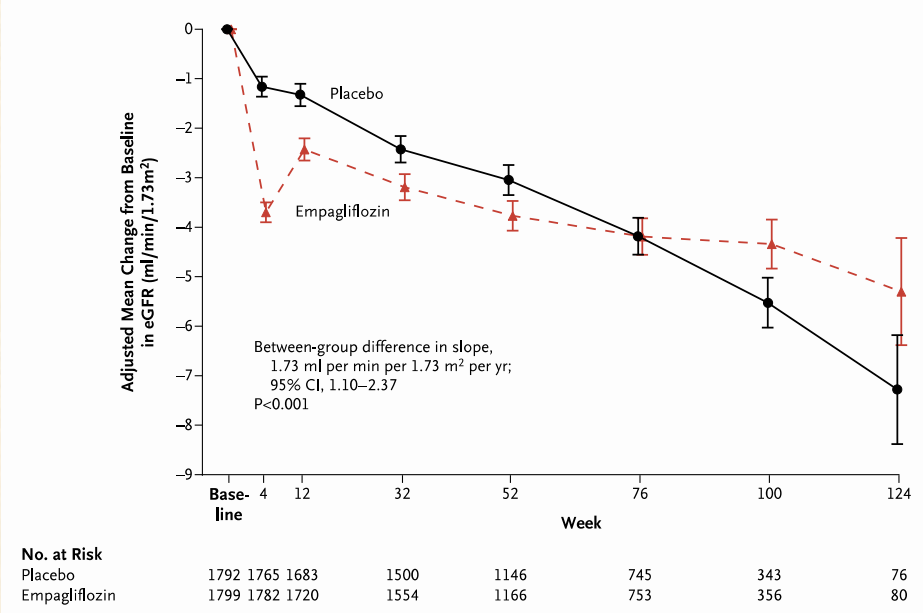


Hospitalization for heart failure in the outcome trials with SGLT2-inhibitors



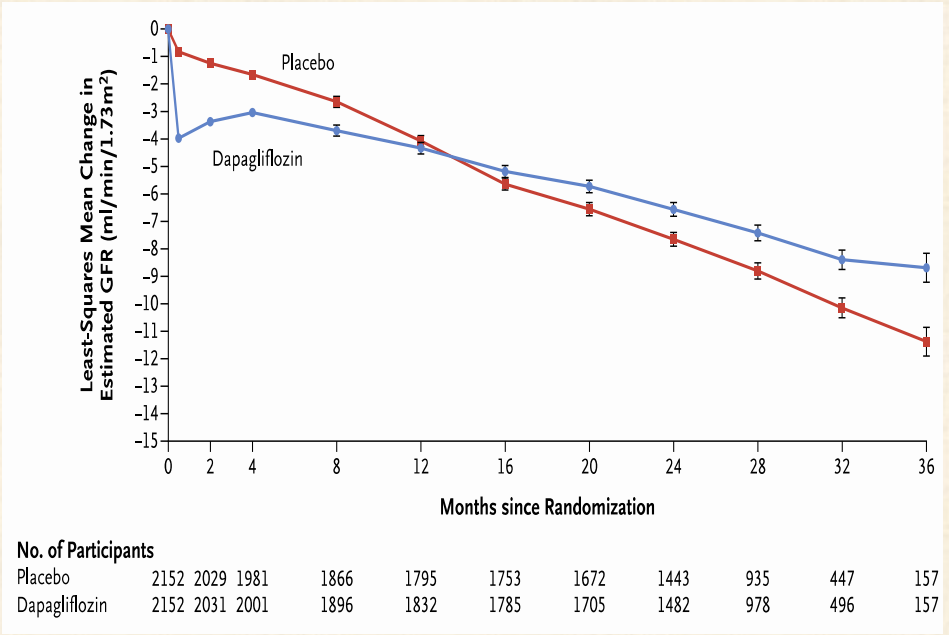
Trajectories of eGFR in the EMPEROR-REDUCED and in the DAPA-CKD trials

EMPEROR-REDUCED



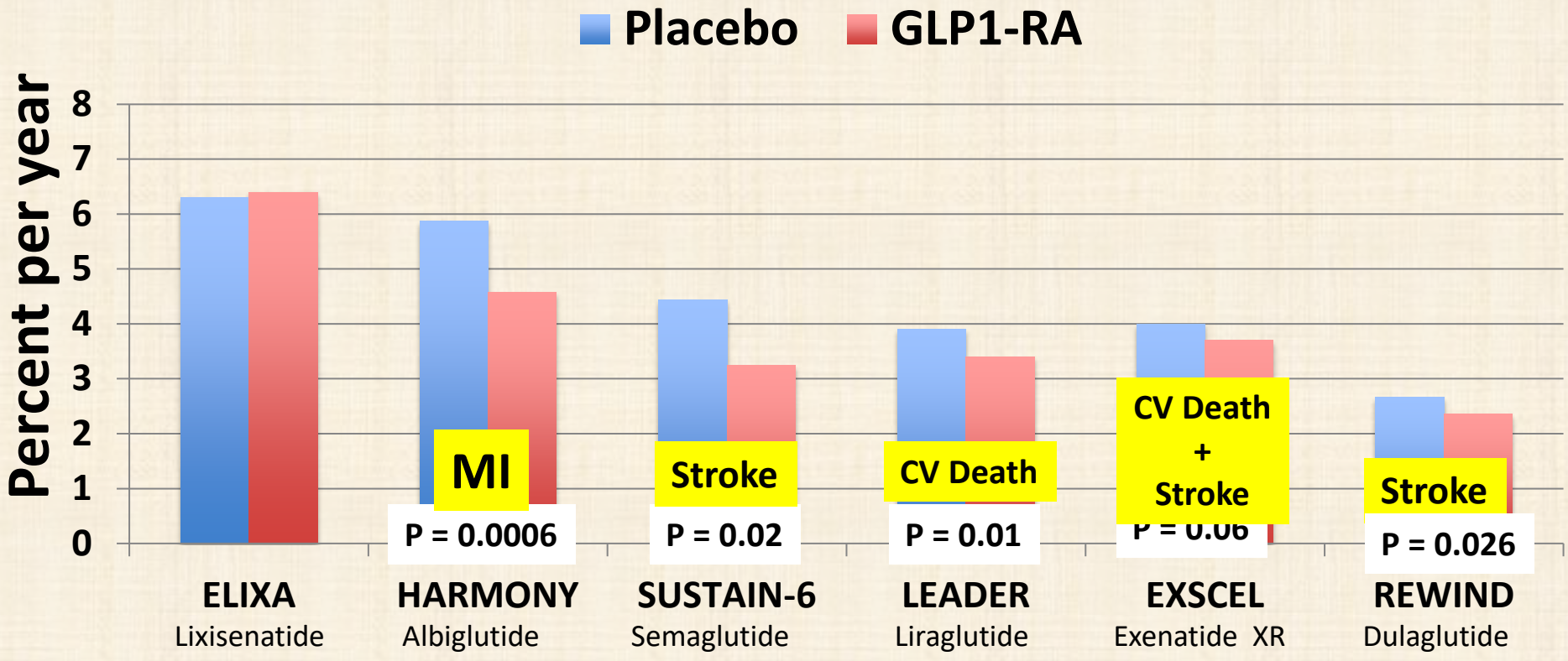
Cannon CP et al.; NEJM 2020

DAPA-CKD

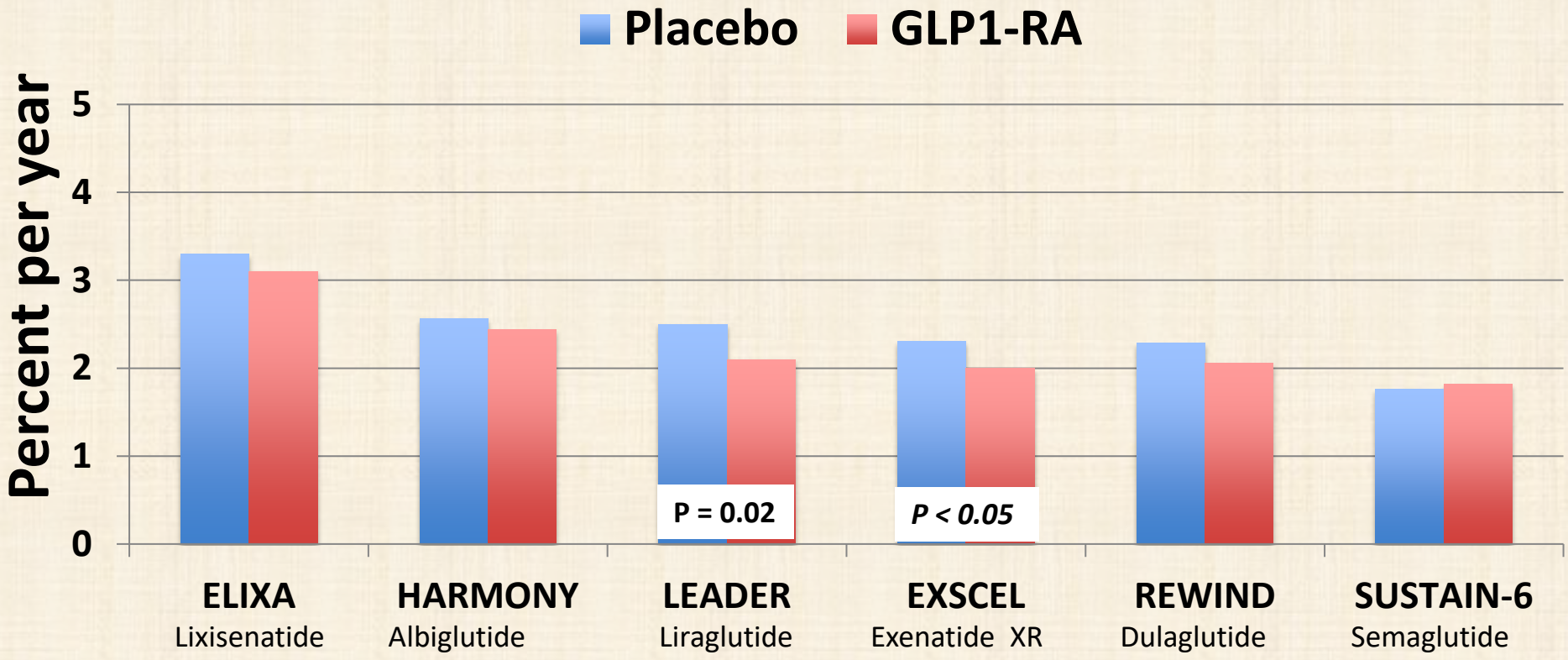


Heerspink HJL et al.; NEJM 2020

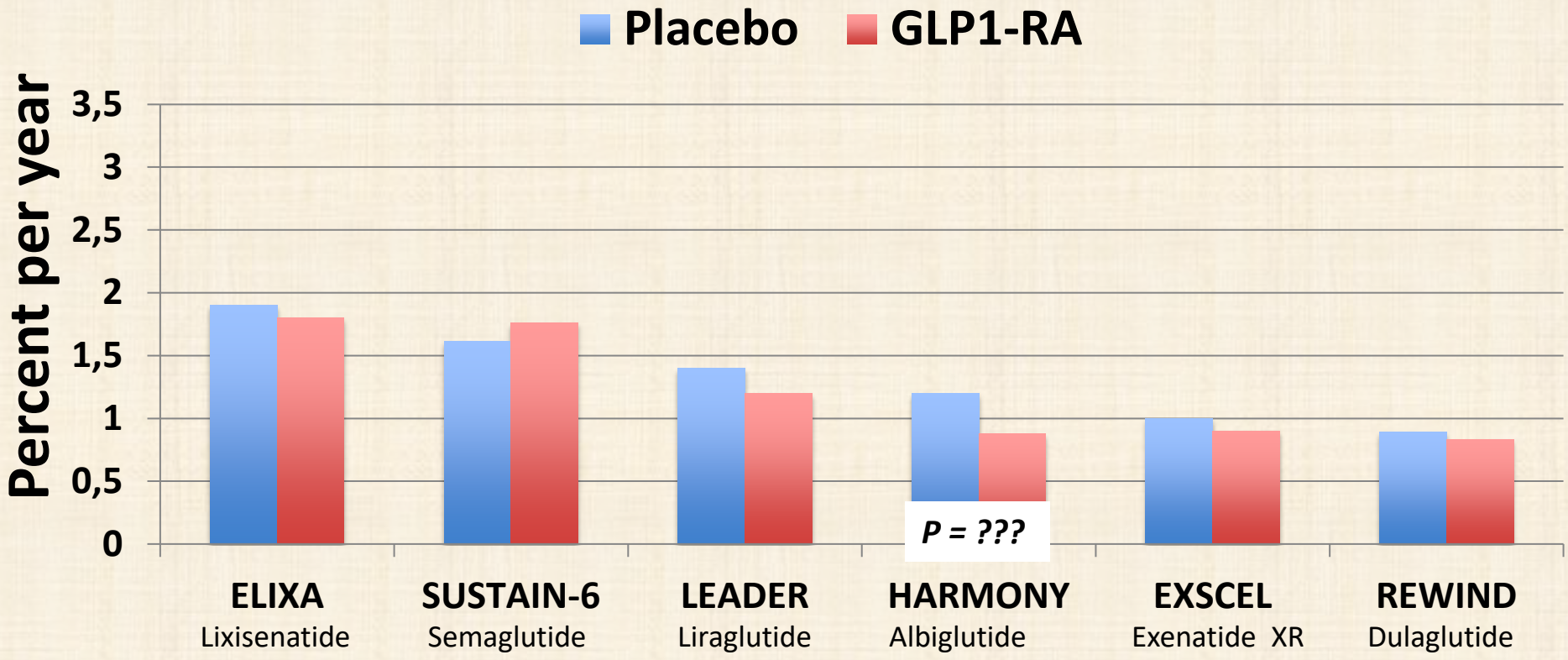
Incidence of MACE in the CVOTs with GLP1-RA



All cause death rate in the CVOTs with GLP1-RA

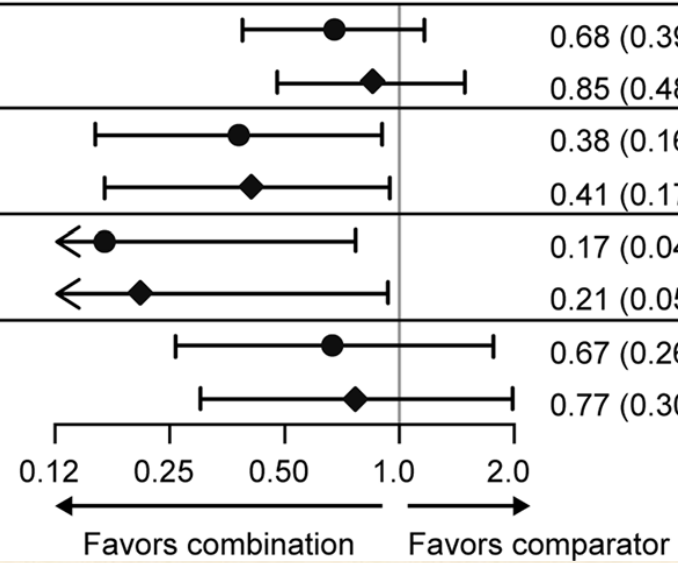


Hospitalization for heart failure in the CVOTs with GLP1-RA



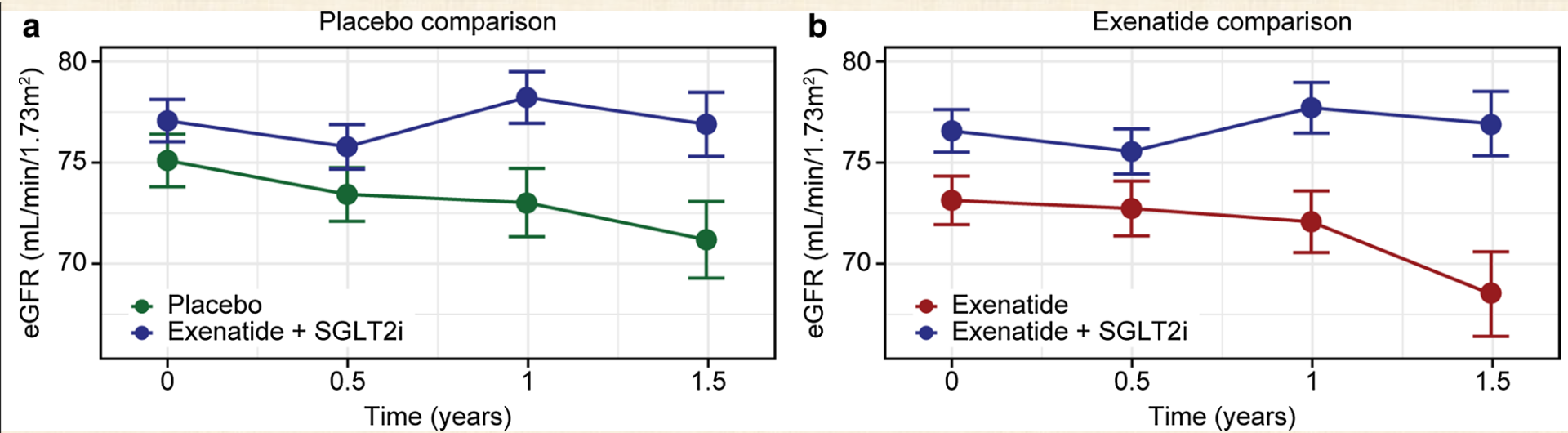
Cardiovascular mortality and safety outcomes with combination weekly exenatide+SGLT2i in the propensity matched cohorts. The EXSCEL trial.

Outcome		Number of events	Combination: Events per 100 pt-yrs	Comparator: Events per 100 pt-yrs	Adjusted hazard ratio (95% CI)
MACE	vs. placebo	57	3.29	4.81	0.68 (0.39-1.17)
	vs. exenatide	54	3.27	4.38	0.85 (0.48-1.49)
All-cause mortality	vs. placebo	30	1.00	2.71	0.38 (0.16-0.90)
	vs. exenatide	32	0.99	2.96	0.41 (0.17-0.95)
CV death	vs. placebo	16	0.28	1.65	0.17 (0.04-0.77)
	vs. exenatide	17	0.28	1.77	0.21 (0.05-0.93)
Serious hypoglycemia	vs. placebo	18	0.94	1.25	0.67 (0.26-1.76)
	vs. exenatide	18	0.93	1.25	0.77 (0.30-1.99)



Clegg LE et al.; Cardiovascul Diabetol 2019

Trajectories of eGFR with combination weekly exenatide+SGLT2i in the propensity matched cohorts. The EXSCEL trial.



Clegg LE et al.; Cardiovascul Diabetol 2019

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Considerazioni conclusive

- **Le attuali evidenze riguardo ad additività/sinergia/complementarietà degli effetti della terapia combinata SGLT2i+GLP1R-A nei pazienti con diabete di tipo 2 sono decisamente incoraggianti**
- **Riguardo alla protezione dal rischio angiocardiorenale, sarebbero utili RCTs ad hoc, che però plausibilmente non verranno mai condotti**
- **Poiché però il rapporto causa-effetto riguardo alla protezione dal danno d'organo (efficacy) è ampiamente provato per ciascuna classe di farmaco, sarà fondamentale condurre studi ad hoc di RWE molto ben disegnati per provare e misurare additività/sinergia/complementarietà di questa protezione nella realtà clinica quotidiana (effectiveness)**
- **Va tenuto sempre in grande considerazione il monito del consensus statement di ADA-EASD di dare la preferenza ai farmaci con "RCT-proven benefit"**

Grazie dell'attenzione