I VANTAGGI DELL'INIZIO PRECOCE DEI FARMACI INNOVATIVI PER IL DIABETE

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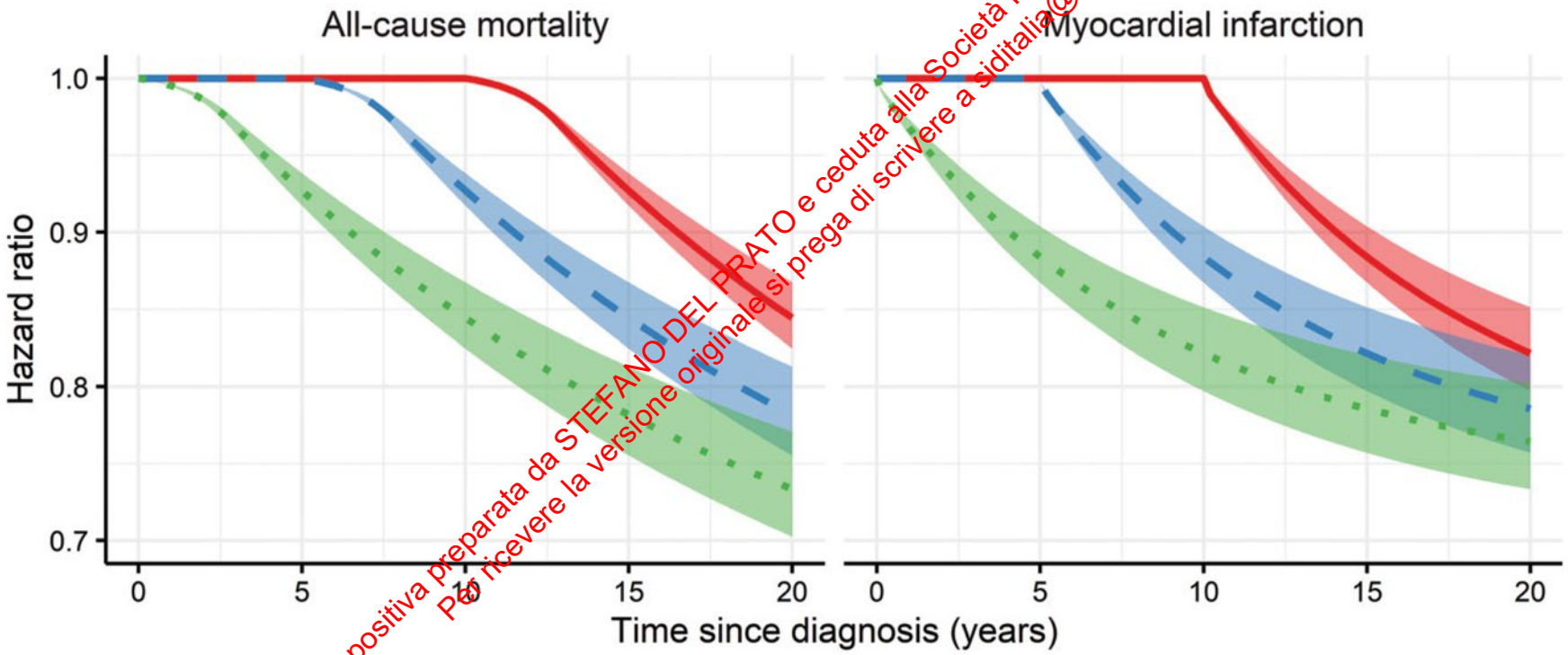
Presenter Disclosures

Research support -	AstraZeneca, Boehringer Ingelheim
Advisory board -	Applied Therapeutics, AstraZeneca, Boheringer Ingelheim, Eli Lilly & Co., GlaxoSmithKline, Merck Sharpe & Dohme, Novartis Pharmaceutical Co., Novo Nordisk, Sanofi
Speaking Engagements -	AstraZeneca, Boehringer Ingelheim, Eli Lilly & Co., Merck Sharpe & Dohme, Novartis Pharmaceutical Co., Novo Nordisk, Sanofi, Takeda Pharmaceuticals

Historical HbA1c Values* May Explain the T2DM Legacy Effect

*assuming a one percentage unit lower HbA1c from diagnosis (■), 5 yrs (■) and 10 yrs (■) from diagnosis

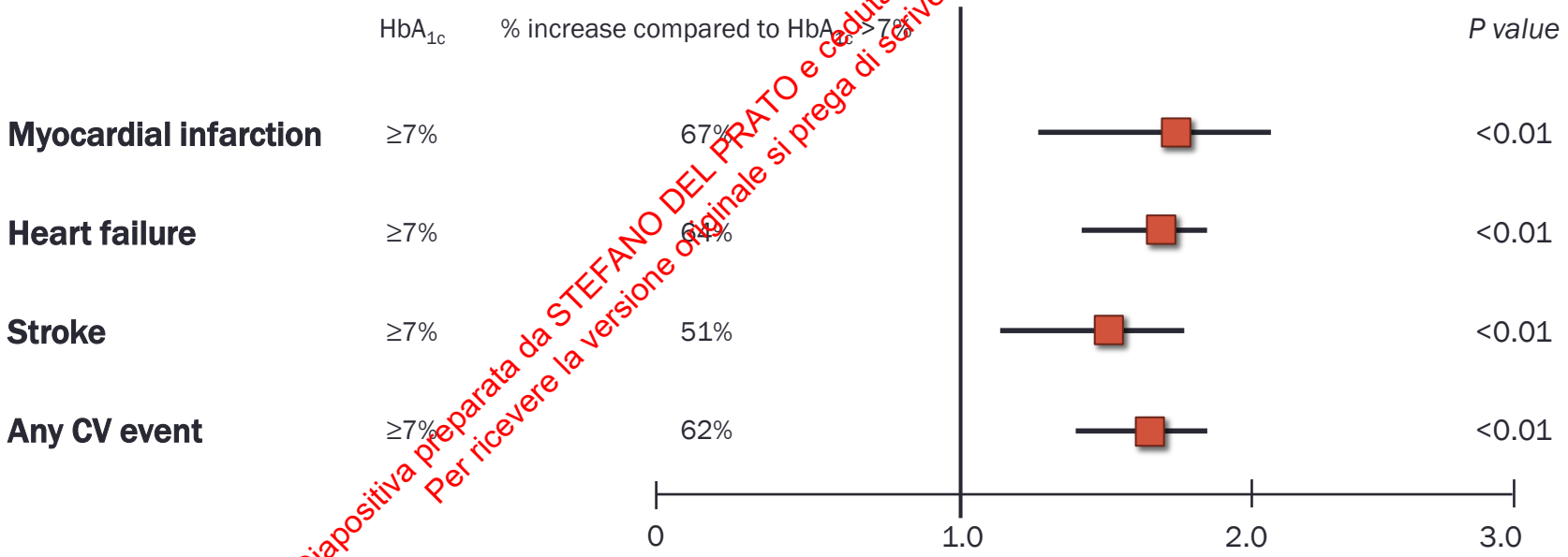


Lind M et al *Diabetes Care* 2021;44:2231–2237

A Delay In Therapy Intensification by 1 Year Increases Cardiovascular Disease by over 60%

Retrospective cohort study based on the UK-CPRD database (n=104,477; Median follow-up: 5.3 years)

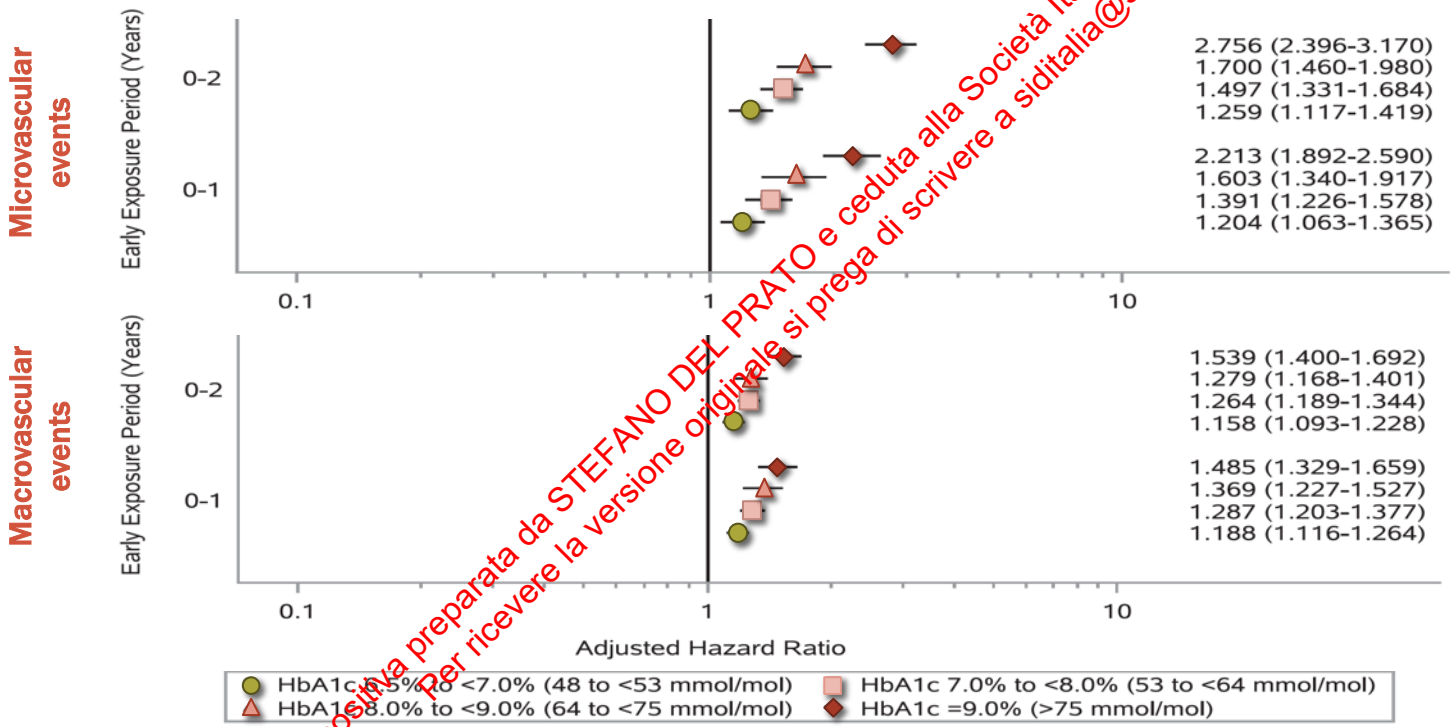
Therapy intensification >1 year in patients with HbA_{1c} ≥7% increased the risk of MI, stroke, HF and composite CVE compared to patients with HbA_{1c} <7% and time to intensification <12 months (reference group)



Paul S. et al. ***Cardiovasc Diabetol*** 2015;14:100

10-yr Risk of Complication for Early HbA1c >6.5%

34,737 managed care newly diagnosed T2DM patients; 10 years of survival (average follow-up 13.0 years)

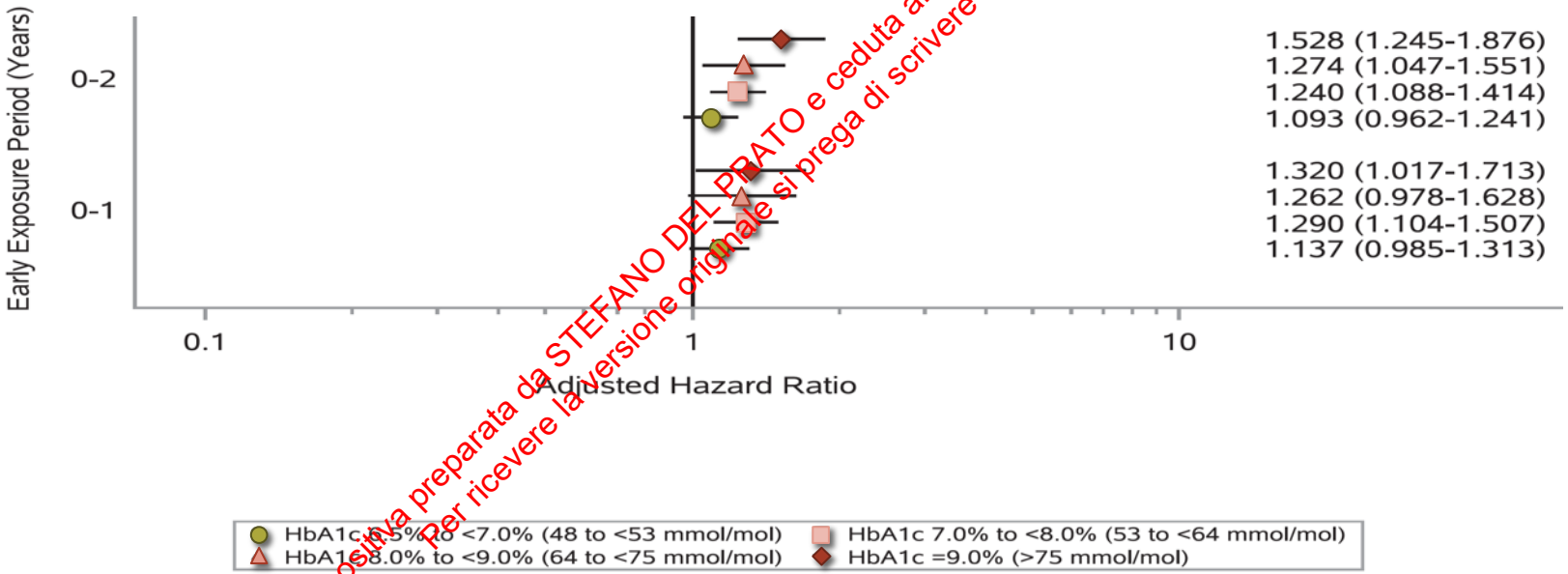


HRs adjusted for year of diagnosis, age at diagnosis, sex, race/ethnicity, BMI, systolic and diastolic blood pressure, total cholesterol, HDL cholesterol, smoking status, HbA1c after each early exposure period, and comorbidity.

Laiteerapong N et al *Diabetes Care* 2019; 42:416-426]

10-yr Mortality Risk for Early HbA1c >6.5%

34,737 managed care newly diagnosed T2DM patients; 10 years of survival (average follow-up 13.0 years)



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Laiteerapong N et al *Diabetes Care* 2019; 42:416-426]

Domanda N. 1

- Il controllo glicemico nella fase immediatamente successiva alla diagnosi è da considerarsi un elemento critico sul rischio di sviluppare complicanze micro- e macro-angiopatiche?
  - **Sì**
  - **No**
  - **Non so**

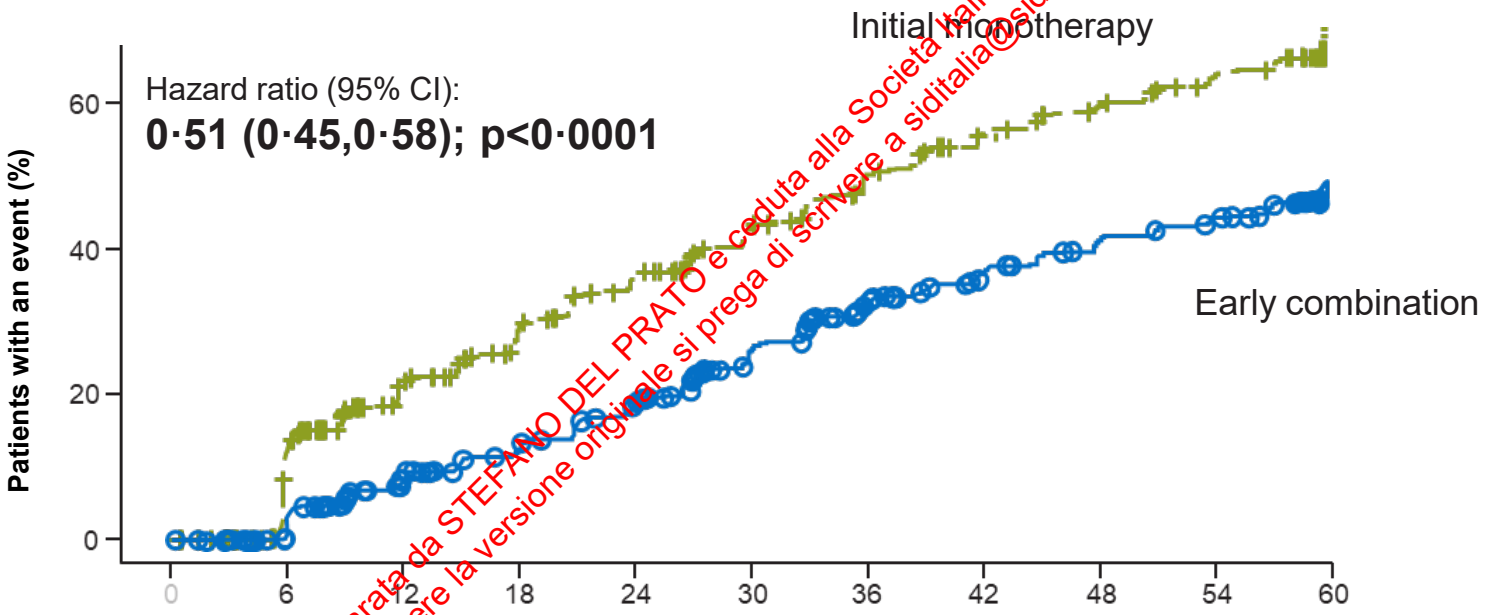
VERIFY - Baseline Characteristics

Variable	Early combination N=998	Initial monotherapy N=1003
Women	55%	51%
Age (years)	54.1 (9.5)	54.6 (9.2)
T2DM duration (months)*	3.3 (1.0–9.8)	3.4 (0.9–10.4)
HbA1c (%)	6.7 (0.4)	6.7 (0.5)
FPG (mmol/L)*	6.9 (6.1–7.8)	6.9 (6.2–7.9)
BMI (kg/m^2)	31.2 (4.8)	31.0 (4.7)
Weight (kg)*	85.0 (72.8–97.3)	84.0 (72.0–97.0)
Normal baseline eGFR (MDRD), ml/min/1.73m^2	43.3%	44.3%
Current smoker	15.4%	13.6%

Data is presented as mean (SD), unless specified.*Median (IQR). The baseline demographics and clinical characteristics were similar between the treatment arms

Matthews DR et al. *Lancet*. 2019; 394:1519-1529

VERIFY - Time to Initial Treatment Failure



Patients at risk

Early combination	983	960	862	815	752	671	597	551	509	478	187
Initial monotherapy	989	937	733	661	576	503	434	377	337	299	108

Matthews DR et al. ***Lancet***. 2019; 394:1519-1529

Time to First Adjudicated Macro-vascular Event

Patients at risk										
Initial monotherapy	967	923	895	875	852	842	824	806	783	710
Early combination	996	970	941	924	912	890	874	846	822	809	731
Number of events										
Initial monotherapy	1	6	9	13	18	22	23	26	27	32	33
Early combination	0	0	3	4	8	10	16	18	20	21	24

Although this is an indicative signal, more dedicated studies are required

Caveat! Small numbers, and wide confidence limits

Matthews DR et al. *Lancet* 2019; 394:1519-1529

CVOTs in DM - Effect of Glucose-Lowering Drugs on 3-Point MACE in T2DM Patients

Study	Glucose-lowering drug	HR	95% CI	*P*-value
SAVOR	Saxagliptin	1.00	0.89 – 1.12	NS
EXAMINE	Alogliptin	0.96	0.80 – 1.15	NS
TECOS	Sitagliptin	0.98	0.89 – 1.08	NS
CARMELINA	Linagliptin	1.02	0.89 – 1.17	NS
CAROLINA	Linagliptin	0.98	0.84 – 1.14	NS

Scirica BM *et al. N Engl J Med* 2013;369:1317; White WB *et al. N Engl J Med* 2013;369:1327; Green JB *et al. N Engl J Med* 2015;373;232; Rosenstock J et al *JAMA* 2019;321:69; Rosenstock J et al *JAMA* 2019;322:2138; Pfeffer MA *et al. N Engl J Med* 2015;373:2247; Zinman B *et al. N Engl J Med* 2015;373:2117; Marso SP *et al. N Engl J Med* 2016;375:311; Marso SP *et al. N Engl J Med* 2016;375:1834; Neal B *et al. N Engl J Med* 2017;377:644; Holman RR *et al N Engl J Med* 2017;377:1228; Hernandez AF *et al. Lancet* 2018;393:1519; Wiviott SD et *NEJM* 2018;380:1881; Husain M et al *NEJM* 2019;381:841; Cannon CP et al 2020; 383:1425-1435; Gerstein H et al *N Engl J Med* 385:896-907

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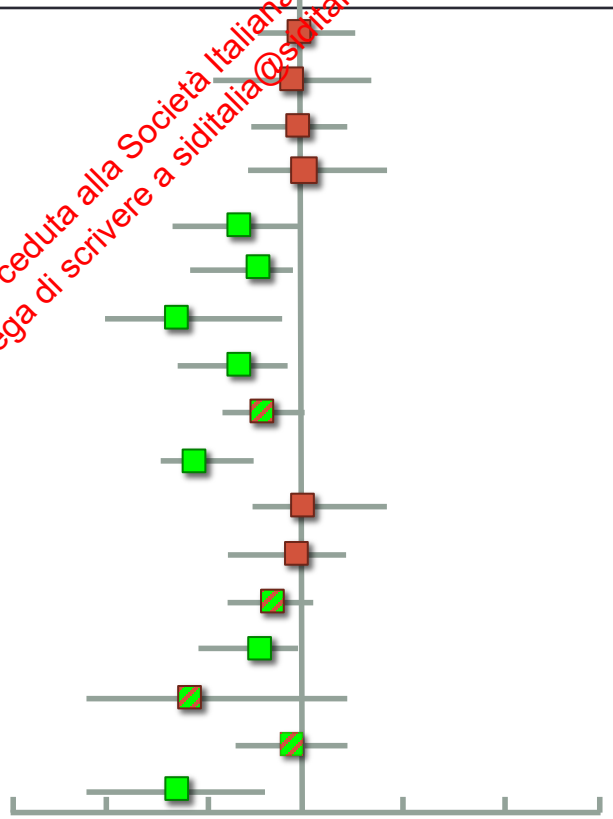
ELIXA	Lixisenatide	1.02	0.89 – 1.17	NS
EMPA-REG	Empagliflozin	0.86	0.74 – 0.99	0.038
LEADER	Liraglutide	0.87	0.78 – 0.97	0.01
SUSTAIN-6	Semaglutide	0.74	0.58 – 0.95	0.02
CANVAS	Canagliflozin	0.86	0.75 – 0.97	0.02
EXSCEL	Exenatide QW	0.91	0.83 – 1.00	0.061
HARMONY	Albiglutide QW	0.78	0.68 – 0.90	0.0006
CARMELINA	Linagliptin	1.02	0.89 – 1.17	NS
CAROLINA	Linagliptin	0.98	0.84 – 1.14	NS
DECLARE	Dapagliflozin	0.93	0.84 – 1.03	0.17
REWIND	Dulaglutide	0.88	0.79 – 0.99	0.026
PIONEER	Oral semaglutide	0.79	0.57 – 1.11	0.17
VERTIS	Ertugliflozin	0.97	0.85 – 1.11	NS
AMPLITUDE-O	Efpeglenatide	0.73	0.58 – 0.92	0.007



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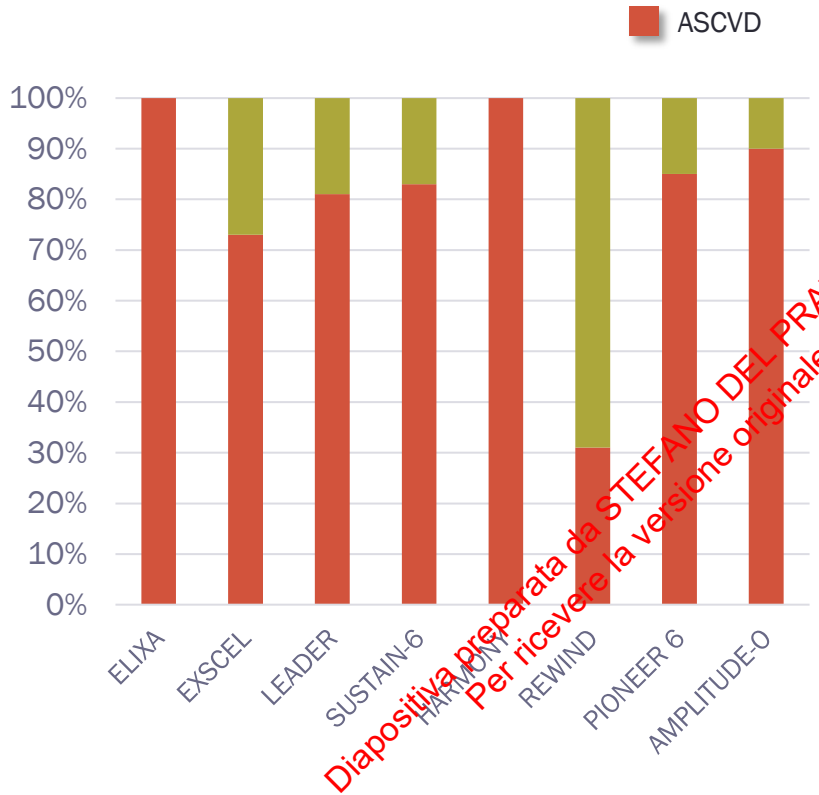
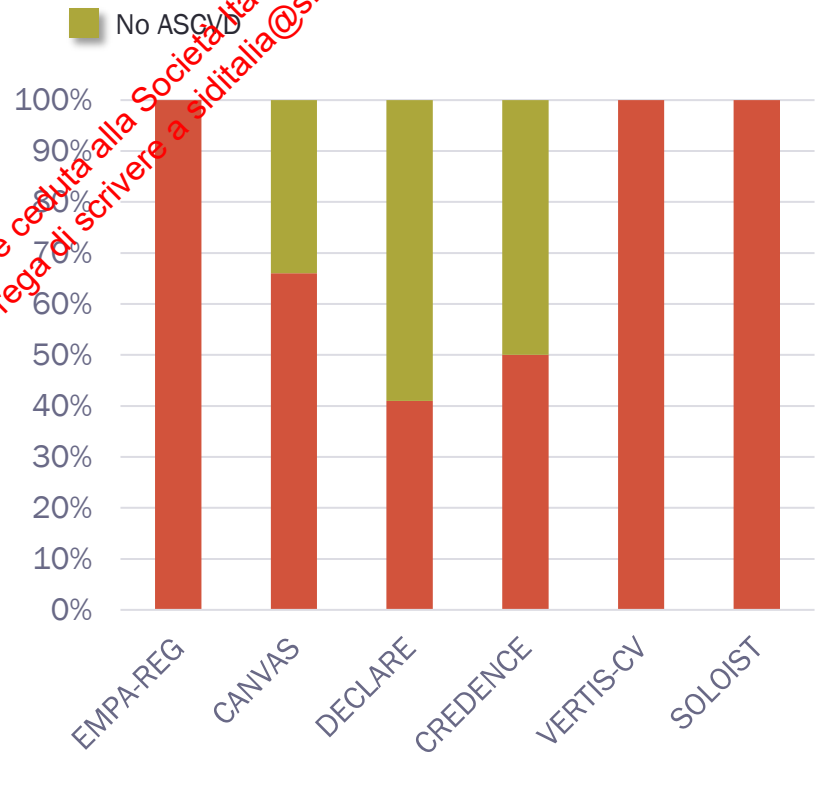
Baseline Prevalence of Established Atherosclerotic CVD across CVOTs

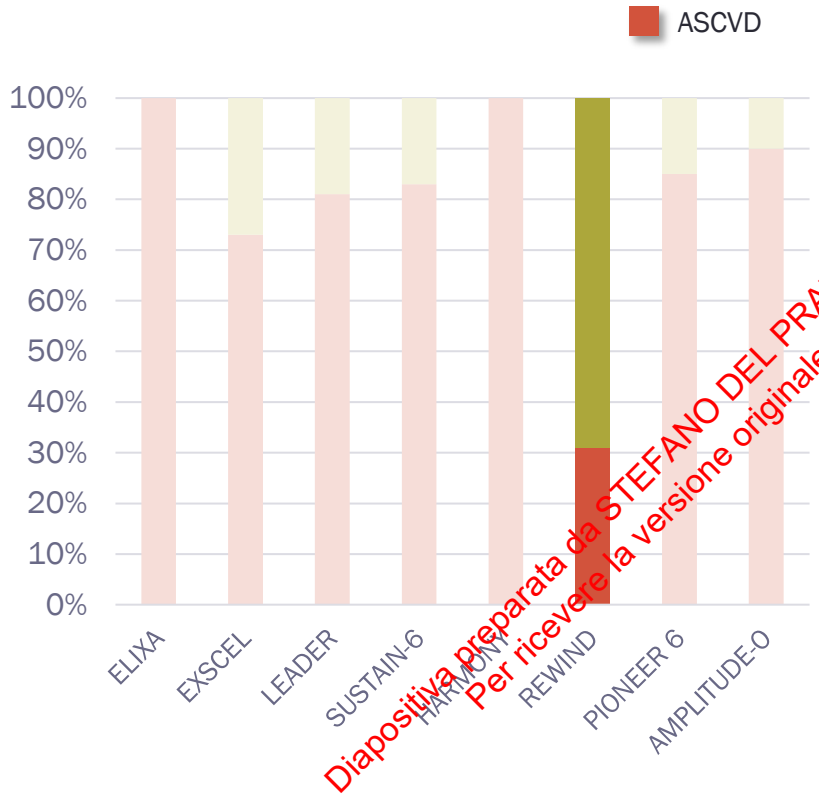


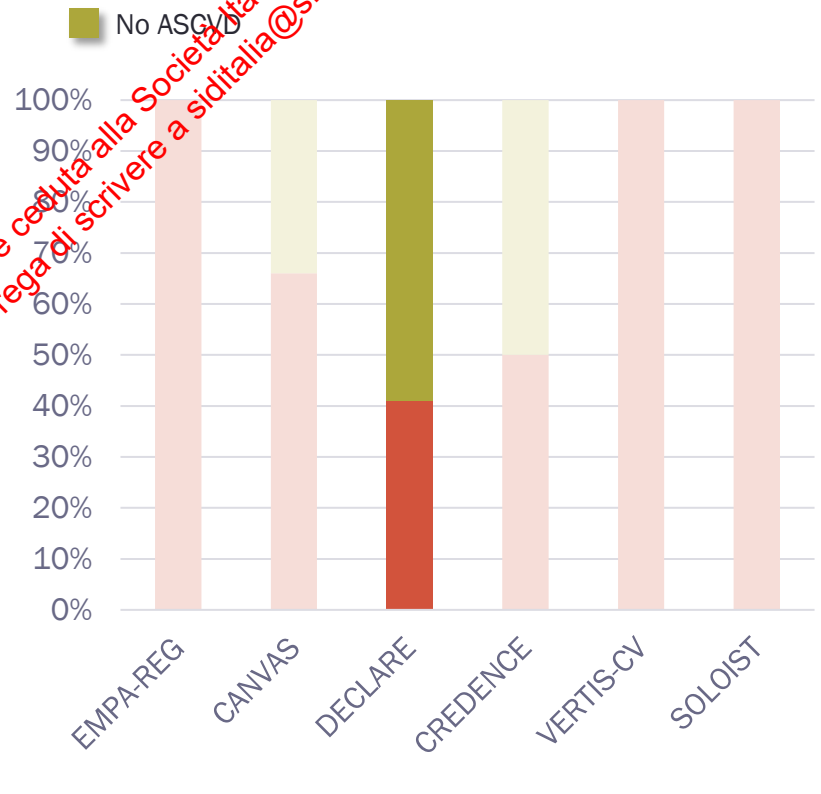
Adapted from Sattar N et al. ***Lancet Diabetes Endocrinol*** 2021; 9: 653-662



Adapted from Pollock C, Neuen BL. ***Adv Chronic Kidney Dis*** 2021; 28: 298-308

Baseline Prevalence of Established Atherosclerotic CVD across CVOTs





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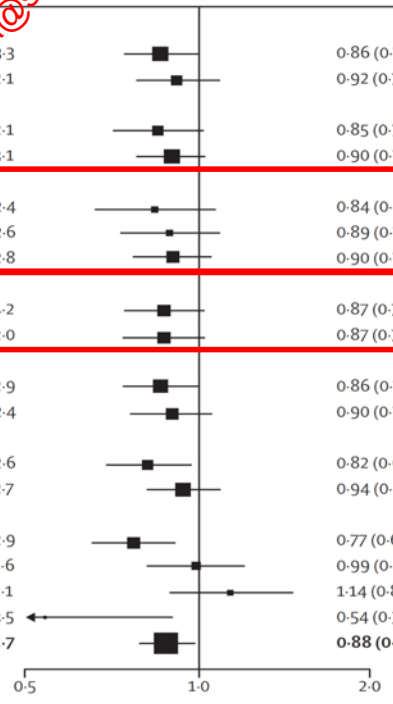
Adapted from Pollock C, Neuen BL. ***Adv Chronic Kidney Dis*** 2021; 28: 298-308

REWIND - CV Composite in Prespecified Subgroups

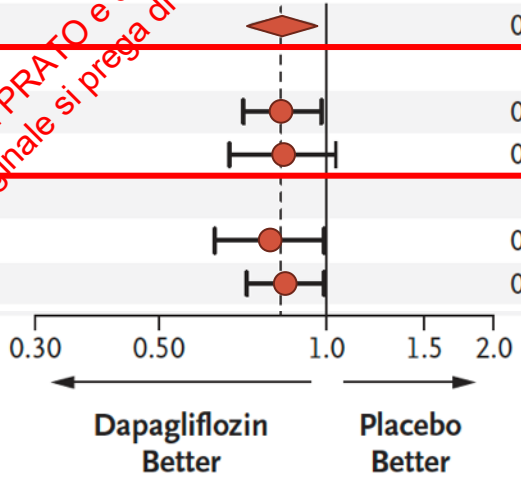
	Dulaglutide		Placebo		Hazard ratio (95% CI)	$p_{interaction}$
	Events/patients (%)	Incidence (per 100 person-years)	Events/patients (%)	Incidence (per 100 person-years)		
Age (years)						0·57
≥66	331/2314 (14·3%)	2·9	384/2351 (16·3%)	3·3	0·86 (0·74–1·00)	
<66	263/2635 (10·0%)	1·9	279/2602 (10·7%)	2·1	0·92 (0·78–1·09)	
Sex						0·60
Female	218/2306 (9·5%)	1·8	249/2284 (10·9%)	2·1	0·85 (0·71–1·02)	
Male	376/2643 (14·2%)	2·8	414/2669 (15·5%)	3·1	0·90 (0·79–1·04)	
Duration of diabetes (years)						0·88
<5	128/1227 (10·4%)	2·0	146/1192 (12·2%)	2·4	0·84 (0·66–1·06)	
5–10	174/1446 (12·0%)	2·3	196/1476 (13·3%)	2·6	0·89 (0·73–1·09)	
≥10	292/2276 (12·8%)	2·5	321/2284 (14·1%)	2·8	0·90 (0·77–1·06)	
History of cardiovascular disease*						0·97
Yes	280/1560 (17·9%)	4·2	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)	
Baseline HbA_{1c}*						0·75
≥7·2%	328/2610 (12·6%)	2·5	373/2603 (14·3%)	2·9	0·86 (0·74–1·00)	
<7·2%	263/2339 (11·3%)	2·2	289/2334 (12·4%)	2·4	0·90 (0·76–1·06)	
BMI (kg/m^2)						0·21
≥32	254/2284 (11·1%)	2·1	308/2302 (13·4%)	2·6	0·82 (0·69–0·96)	
<32	340/2687 (12·7%)	2·5	355/2650 (13·4%)	2·7	0·94 (0·81–1·09)	
Region						0·0080
Europe	248/2174 (11·4%)	2·2	315/2165 (14·5%)	2·9	0·77 (0·65–0·90)	
Latin America	191/1511 (12·6%)	2·6	190/1510 (12·6%)	2·6	0·99 (0·81–1·21)	
USA and Canada	132/1032 (12·8%)	2·4	117/1039 (11·3%)	2·1	1·14 (0·89–1·47)	
Asia Pacific	23/232 (9·9%)	1·9	41/238 (17·2%)	3·5	0·54 (0·32–0·89)	
Overall	**594/4949 (12·0%)**	**2·4**	**663/4952 (13·4%)**	**2·7**	**0·88 (0·79–0·99)**	**NA**



Gerstein HC et al. ***Lancet***. 2019; 394:121-130

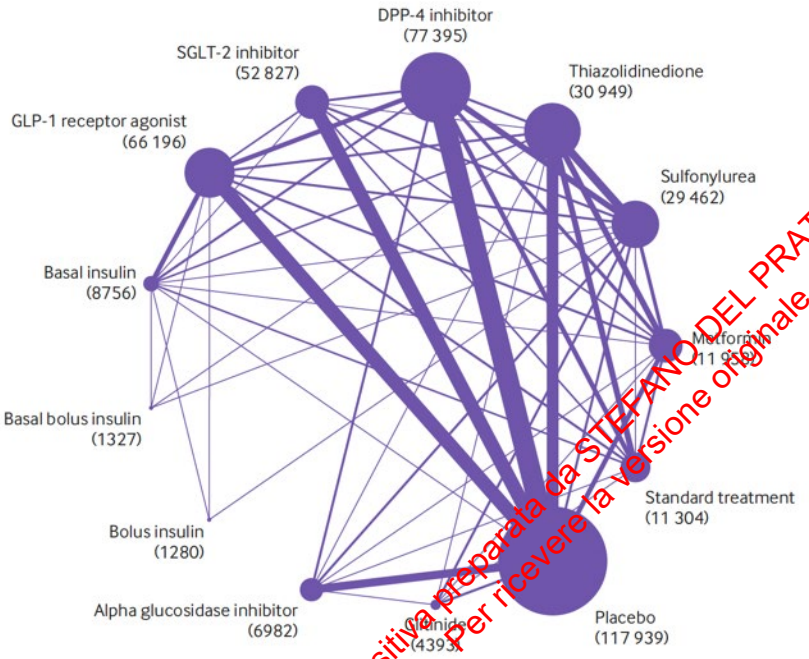
DECLARE - CV Composite in Prespecified Subgroups

Subgroup	Dapagliflozin	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	no. of events/no. of patients			
Total cohort	417/8582	496/8578	0.83 (0.73–0.95)	
Risk group				0.99
ASCVD	272/3474	325/3500	0.83 (0.71–0.98)	
MRF	145/5108	171/5078	0.84 (0.67–1.04)	
History of heart failure				0.60
Yes	142/852	172/832	0.79 (0.63–0.99)	
No	275/7730	324/7706	0.84 (0.72–0.99)	



Wiviott SD et al *N Engl J Med* 2019;380:347-57

SGLT2i and GLP-1RAs for T2DM: Systematic Review and Network Meta-analysis of Randomised Controlled Trials

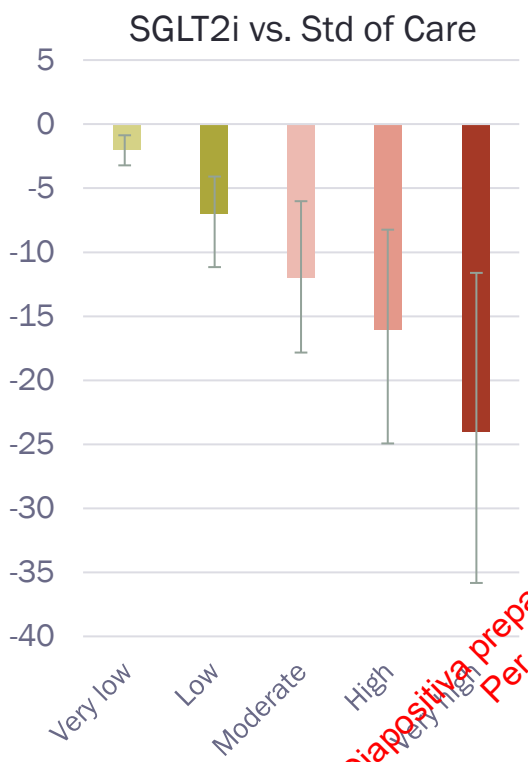


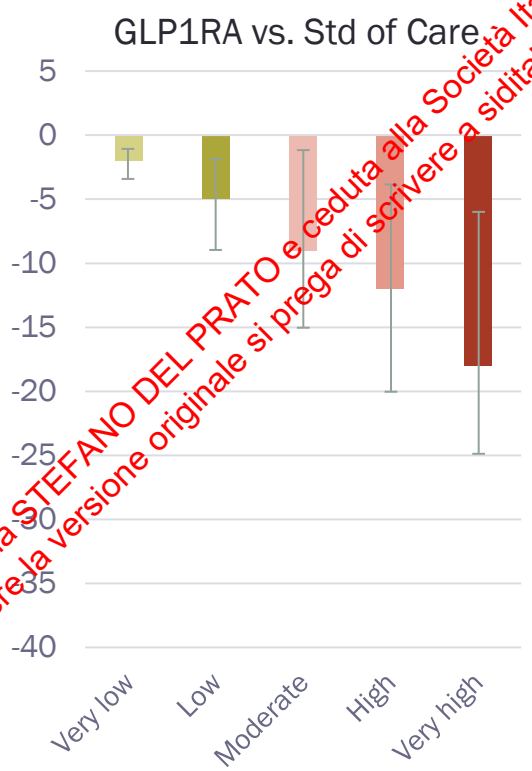
Risk Stratification

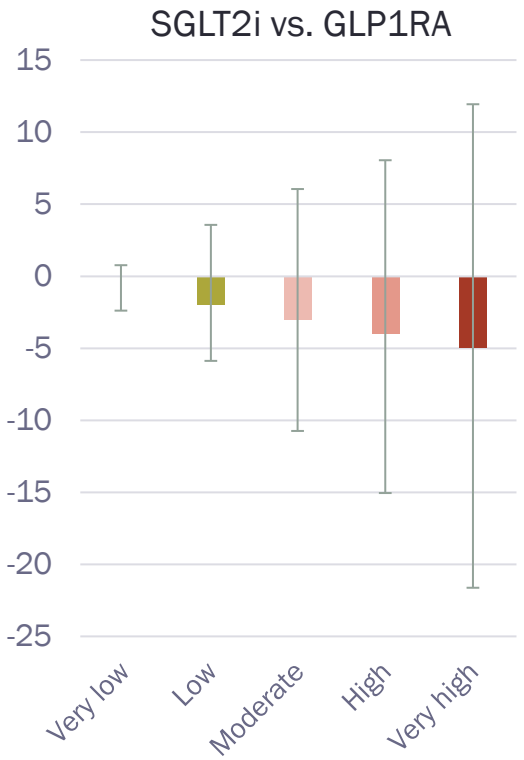
- Very low — no or <3 CV risk factors
- Low — ≥ 3 CV risk factors
- Moderate — CV disease
- High — CKD
- Very high — CVD + CKD

Palmer SC et al *BMJ* 2021; 372:m4573

Anticipated Differences per 1000 T2DM Patients over 5 -yr Treatment in CV Mortality

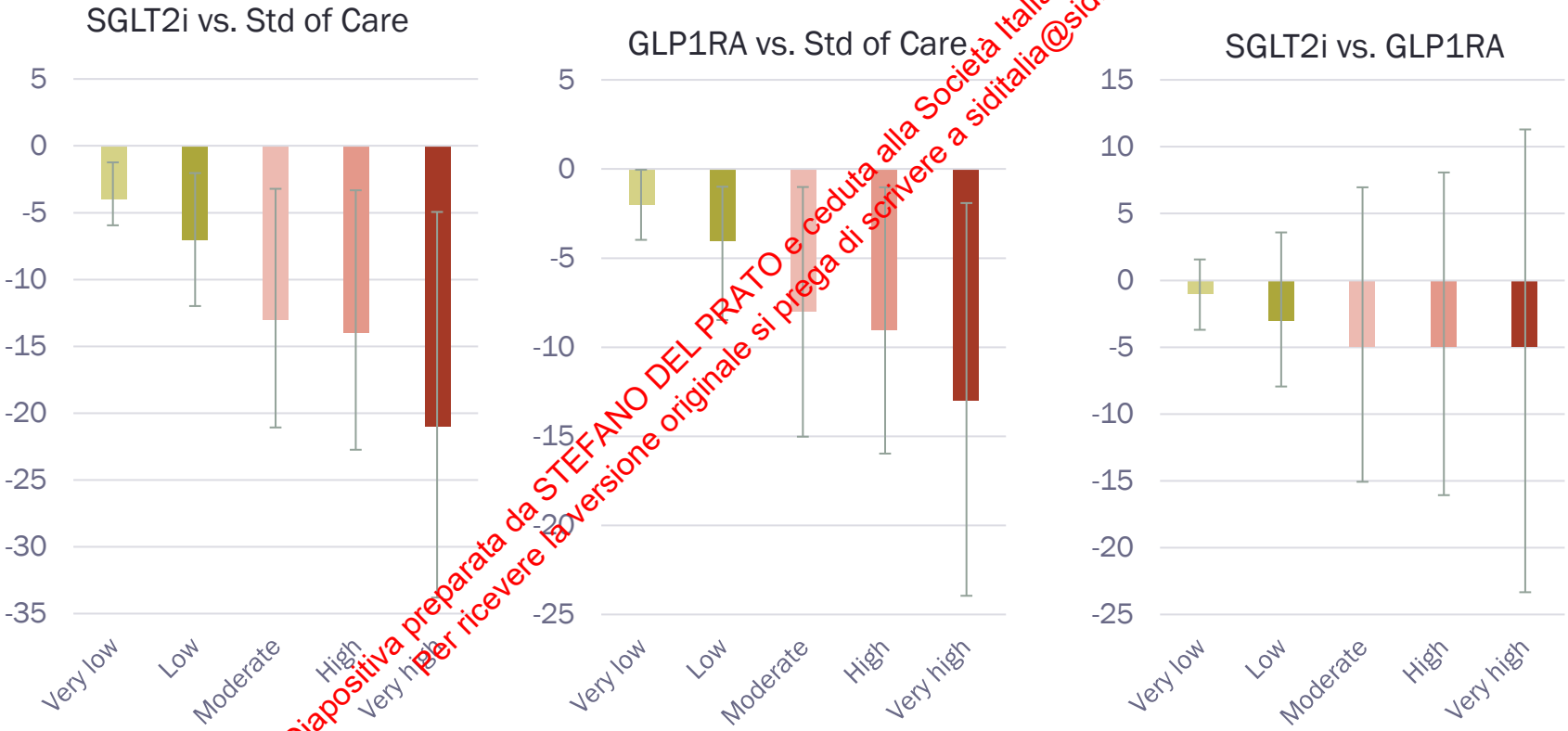






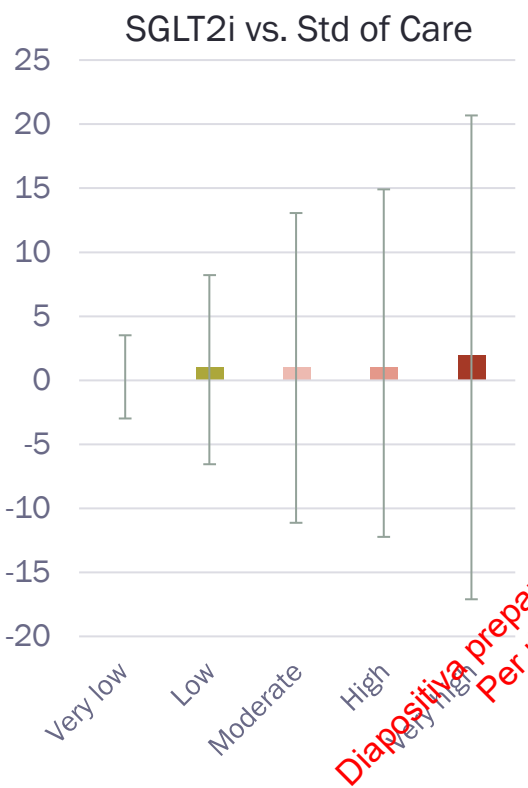
Palmer SC et al *BMJ* 2021; 372:m4573

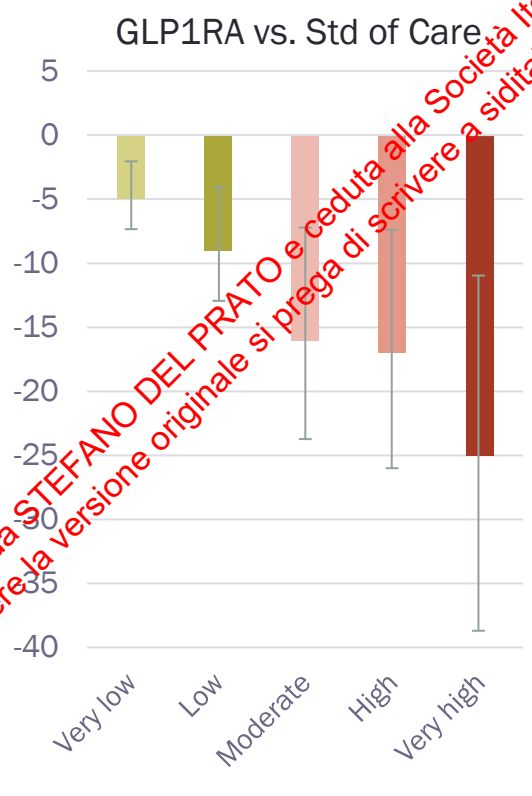
Anticipated Differences per 1000 T2DM Patients over 5 -yr Treatment in Non-fatal Myocardial Infarction

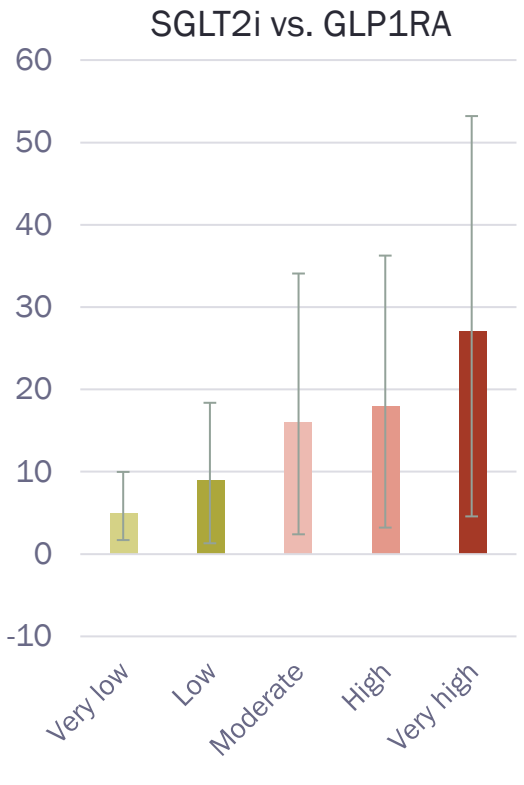


Palmer SC et al *BMJ* 2021; 372:m4573

Anticipated Differences per 1000 T2DM Patients over 5 -yr Treatment in Non-fatal Stroke

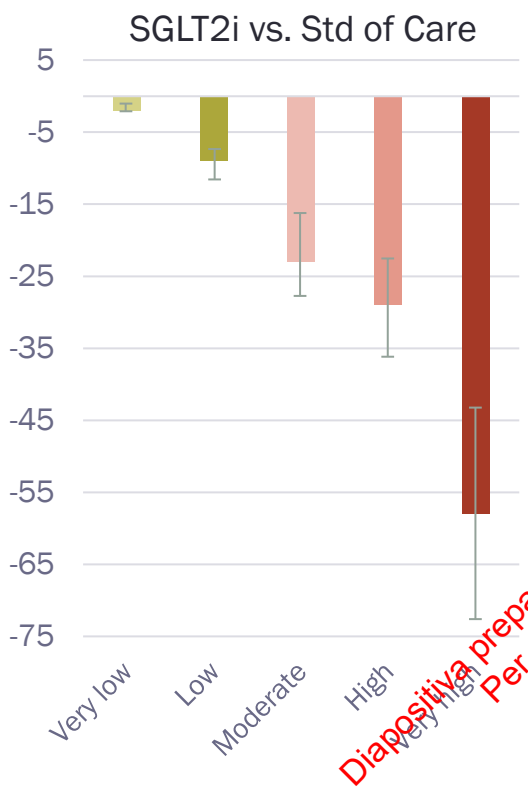


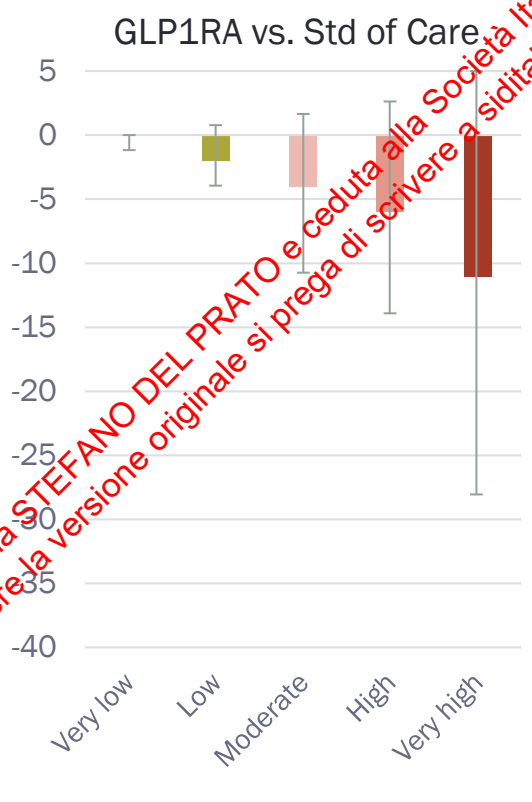


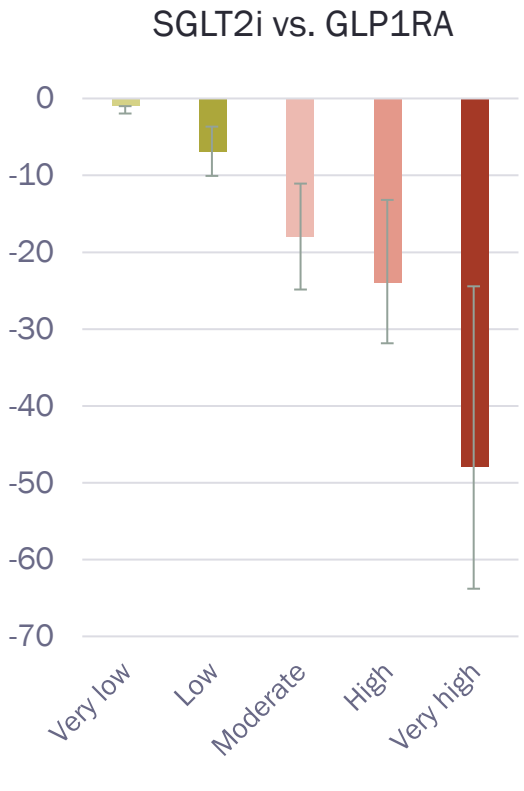


Palmer SC et al *BMJ* 2021; 372:m4573

Anticipated Differences per 1000 T2DM Patients over 5 -yr Treatment in Hospitalization for Heart Failure





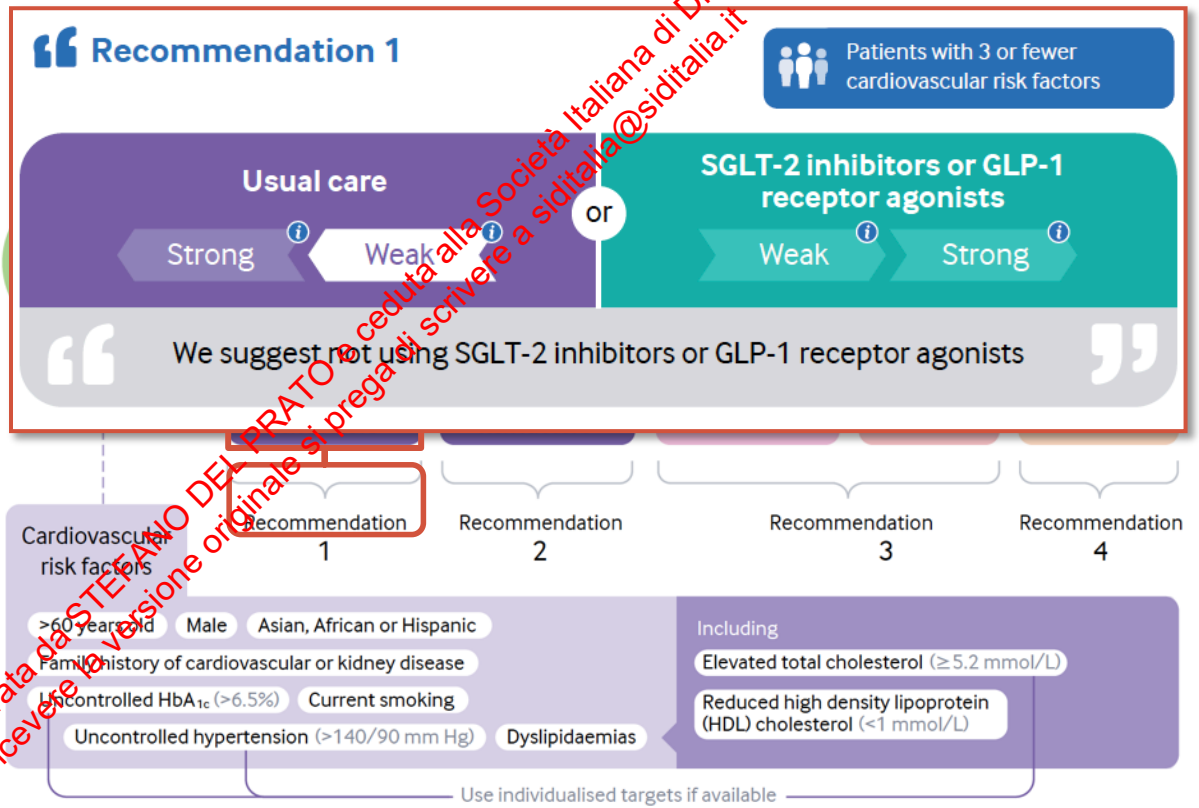


Palmer SC et al *BMJ* 2021; 372:m4573

Domanda N. 2

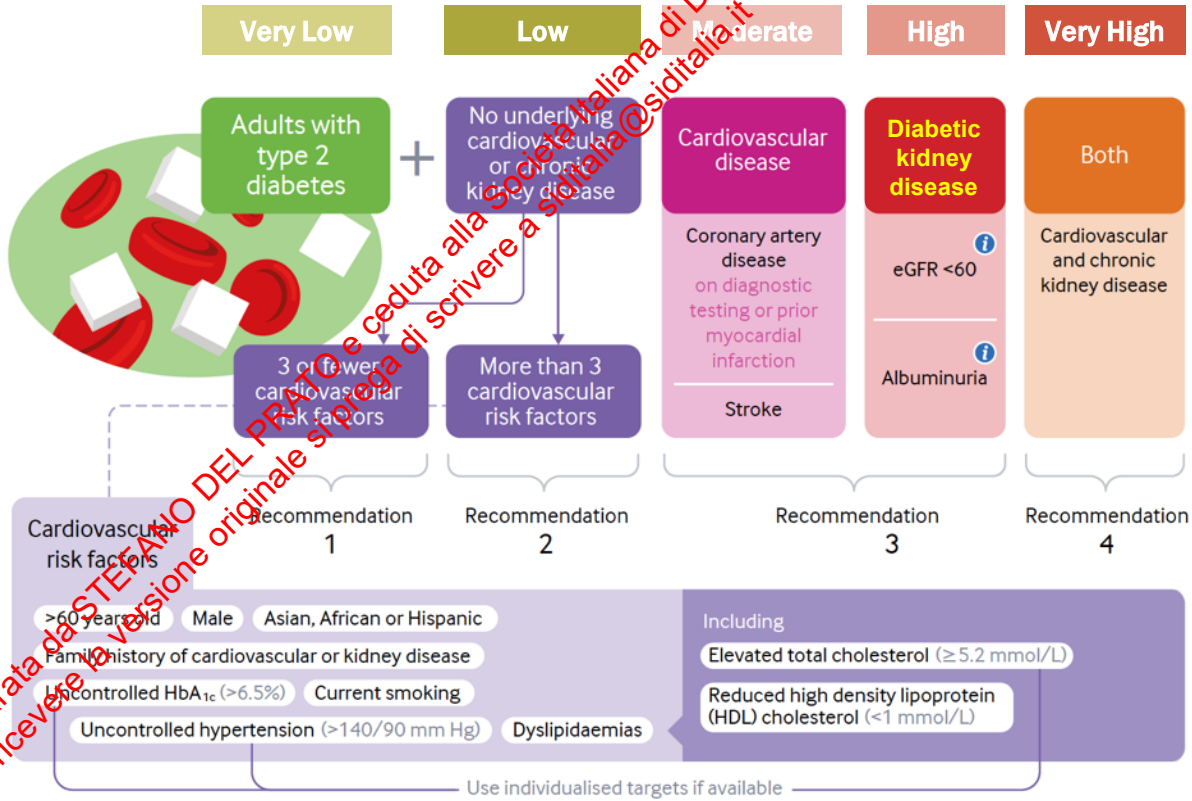
- Le evidenze disponibili sostengono l'impiego precoce dei nuovi farmaci per la prevenzione a lungo termine delle complicanze nel diabete tipo 2?
  - **Sì**
  - **No**
  - **Non so**

SGLT-2i or GLP-1 RAs for Adults with T2DM: A Clinical Practice Guideline



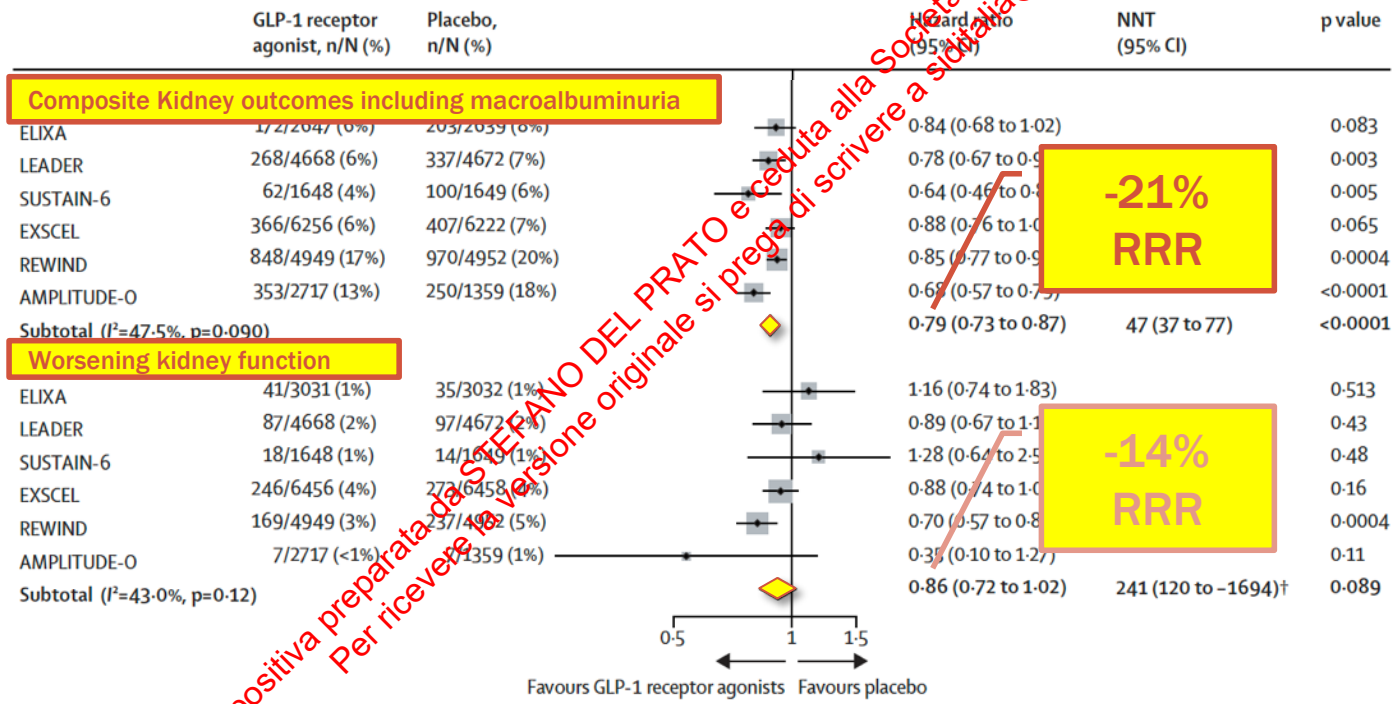
Li S et al *BMJ* 2021;373:n1092

SGLT-2i or GLP-1 RAs for Adults with T2DM: A Clinical Practice Guideline



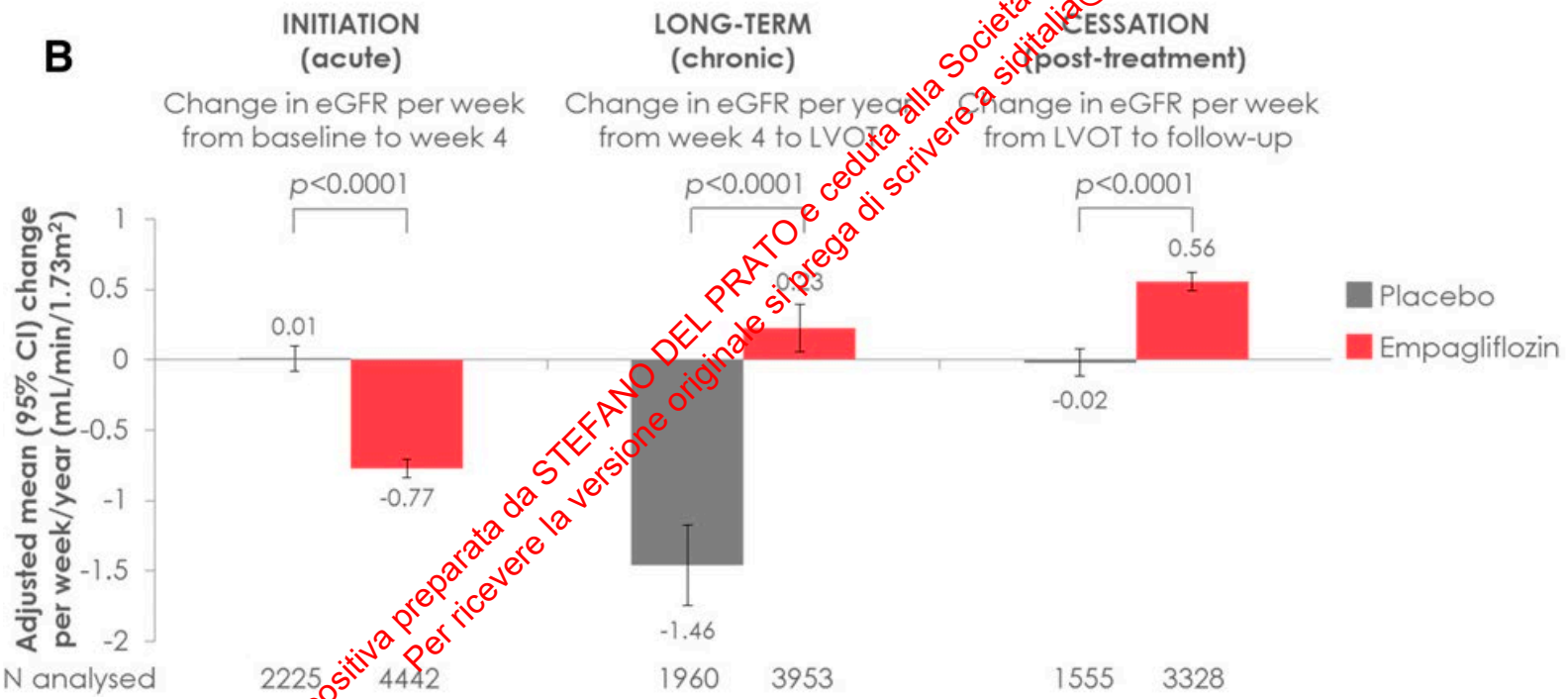
Li S et al *BMJ* 2021;373:n1092

Risk of MACE and Each of its Components with GLP-1 Receptor Agonists in T2DM Patients



Sattar N et al *Lancet Diabetes Endocrinol* 2021;9: 653-662

Empagliflozin and Kidney Function Decline in T2DM Patients: A Slope Analysis from the EMPA-REG OUTCOME Trial

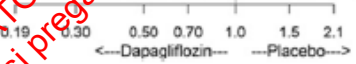


Wanner C et al *J Am Soc Nephrol* 2018; 29: 2755–2769

HF Hospitalization and , Renal-specific Outcomes of Dapagliflozin vs Placebo in a Primary CV Prevention Cohort: Analyses from DECLARE-TIMI 58

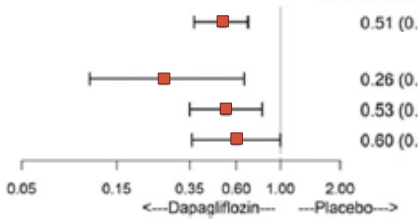
Hospitalization for heart failure

Subgroup	Dapagliflozin n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	interaction p-value
Overall	61/5108 (1.2)	94/5078 (1.9)	0.64 (0.46-0.88)	
eGFR (CKD-EPI) mL/min/1.73 m^2				
<60	6/325 (1.8)	10/297 (3.4)	0.53 (0.19-1.46)	0.854
60-90	30/2281 (1.3)	49/2313 (2.1)	0.61 (0.39-0.96)	
≥ 90	25/2501 (1.0)	35/2468 (1.4)	0.71 (0.42-1.18)	



Renal-specific outcome

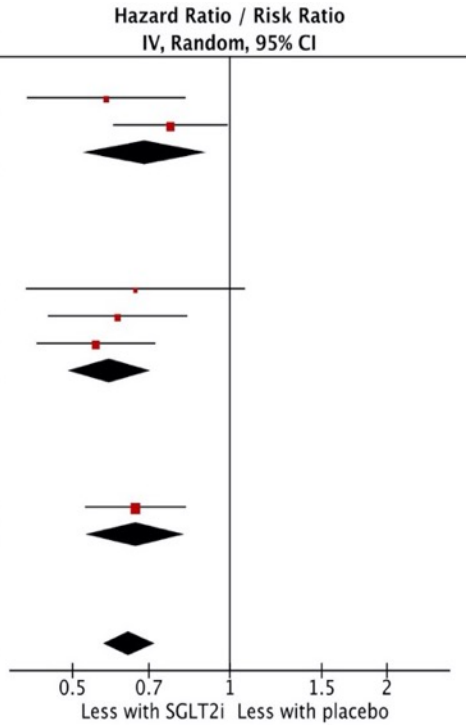
Subgroup	Dapagliflozin n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	interaction p-value
Overall	62/5108 (1.2)	120/5078 (2.4)	0.51 (0.37-0.69)	
eGFR (CKD-EPI) mL/min/1.73 m^2				
<60	6/325 (1.8)	20/297 (6.7)	0.26 (0.11-0.66)	0.269
60-90	31/2281 (1.4)	62/2313 (2.7)	0.53 (0.35-0.81)	
≥ 90	23/2501 (0.9)	38/2468 (1.5)	0.60 (0.36-1.00)	



Adapted from Cahn A et al *Diabetes Care*. 2021 Mar 2:dc202492. doi: 10.2337/dc20-2492. Online ahead of print.

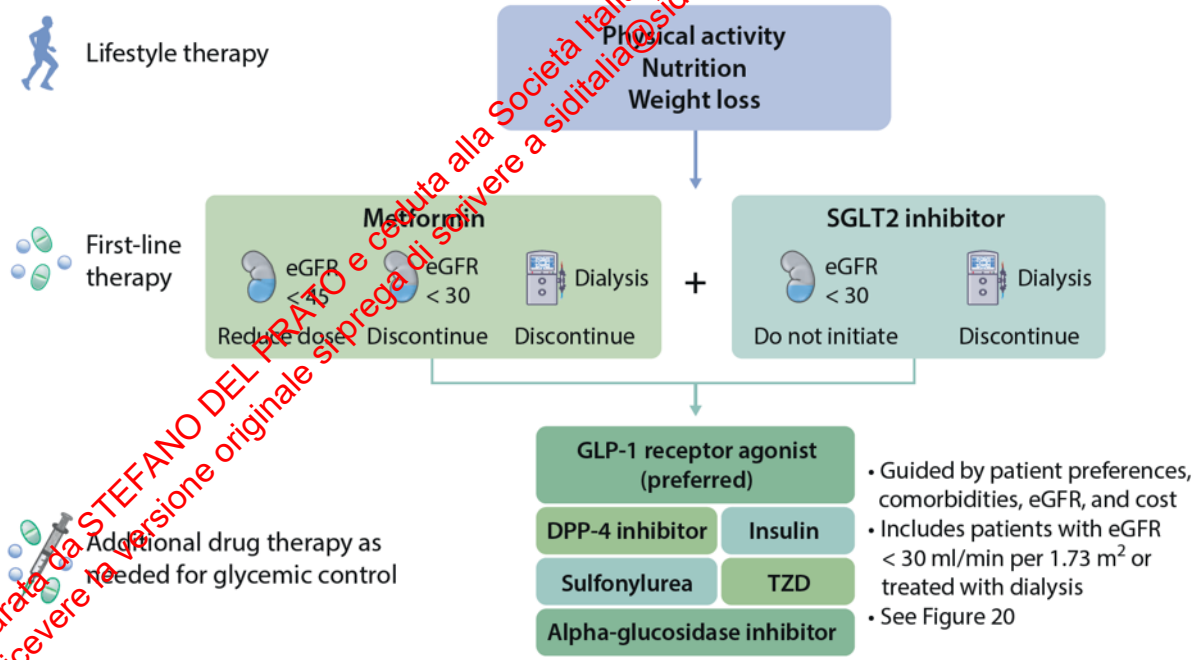
SGLT2-inhibitors and CKD Progression

Study or Subgroup	log[Hazard Ratio / Risk Ratio]	SE	Experimental Total	Control Total	Weight	Hazard Ratio / Risk Ratio IV, Random, 95% CI
1.7.1 Stage 1–2 CKD						
CANVAS Proram (CANVAS / CANVAS-R) 2017	−0.5447	0.177	2813	2811	11.0%	0.58 [0.41, 0.82]
DECLARE-TIMI 58	−0.2614	0.1273	3838	3894	21.4%	0.77 [0.60, 0.99]
Subtotal (95% CI)			**6651**	**6705**	**32.4%**	**0.69 [0.52, 0.90]**
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 1.69$, df = 1 (P = 0.19); $I^2 = 41\%$						
Test for overall effect: Z = 2.71 (P = 0.007)						
1.7.2 Stage 3–5 CKD						
EMPA-REG OUTCOME 2013	−0.416	0.245	1192	605	5.8%	0.66 [0.41, 1.07]
CANVAS Proram (CANVAS / CANVAS-R) 2017	−0.4943	0.1552	1120	929	14.4%	0.61 [0.45, 0.83]
DECLARE-TIMI 58	−0.5903	0.1322	4444	4553	19.8%	0.55 [0.43, 0.72]
Subtotal (95% CI)			**6750**	**6087**	**39.9%**	**0.59 [0.49, 0.71]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.48$, df = 2 (P = 0.79); $I^2 = 0\%$						
Test for overall effect: Z = 5.70 (P < 0.00001)						
1.7.3 All stage CKD						
CREDENCE 2019	−0.4155	0.1119	2202	2199	27.6%	0.66 [0.53, 0.82]
Subtotal (95% CI)			**2202**	**2199**	**27.6%**	**0.66 [0.53, 0.82]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.71 (P = 0.0002)						
Total (95% CI)			**15603**	**14991**	**100.0%**	**0.64 [0.57, 0.72]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.79$, df = 5 (P = 0.58); $I^2 = 0\%$						
Test for overall effect: Z = 7.53 (P < 0.00001)						
Test for subgroup differences: $Chi^2 = 1.09$, df = 2 (P = 0.58), $I^2 = 0\%$						



From 2020 Diabetes Guidelines Speaker's Guide https://kdigo.org/guidelines/diabetes-ckd/ Accessed on March 9 2021

Treatment Algorithm for Selecting Antihyperglycemic Drugs for Patients with T2DM and CKD



Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. ***Kidney Int***. 2020;98:S1-S115.

Combining Glycemic Control and Organ Damage Prevention

Prefer glucose-lowering agents with low risk of hypo and BW gain

Better adherence
Less clinical inertia

Long-term Glycemic control

Prevent Microvascular Complications

Prevent Macrovascular Complications

Combining Glycemic Control and Organ Damage Prevention

Prefer glucose-lowering agents with low risk of hypo and BW gain with ancillary non-glucose properties

Better adherence
Less clinical inertia

Sustained long-term Glycemic control

Prevent Microvascular Complications

Prevent Macrovascular Complications


Diapositiva preparata da STEFANO DEL PRATO e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

PEACE, PROSPERITY, PROGRESS