Prevenzione e terapia dello scompenso cardiometabolico: SGLT2i, GLP-1RA o entrambi?

Paolo Fiorina, MD PhD

University of Milan
Fatebenefratelli-Sacco-Melloni Hospitals, Milan

Outline

1. Introduction
2. SGLT2i
3. GLP-1RA
4. Combination therapy
5. Conclusions

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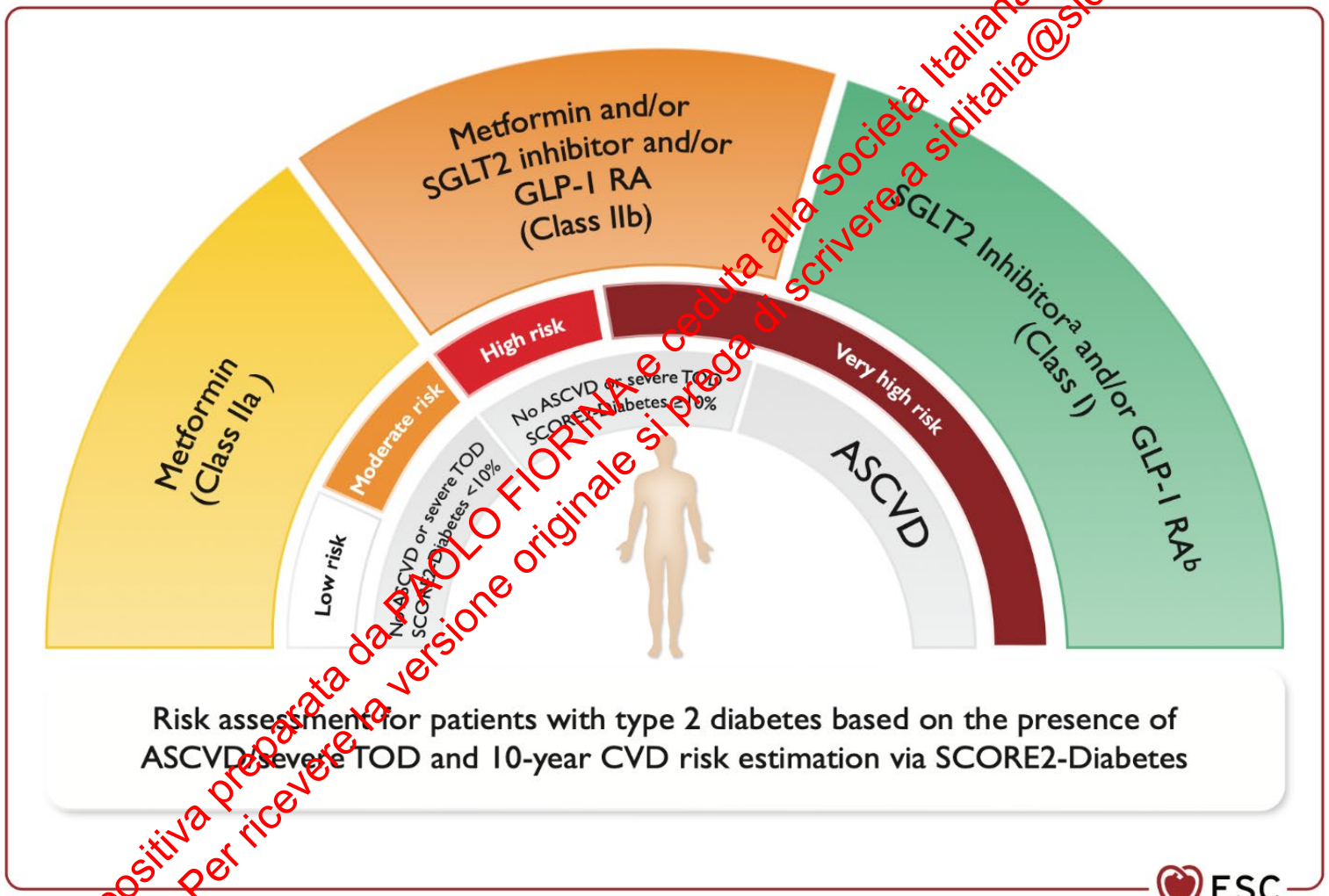
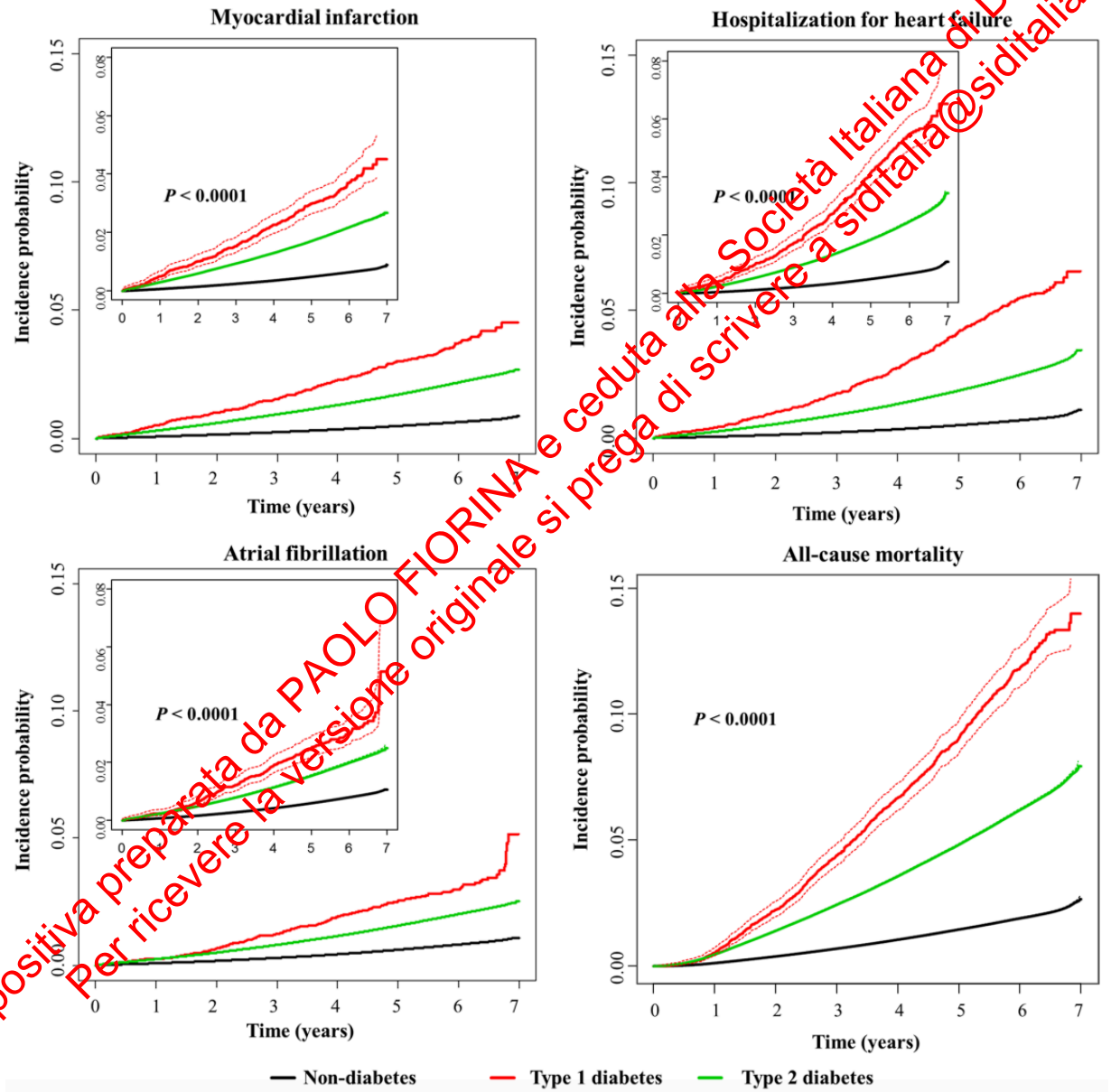
ESC guidelines 2023 for CVD



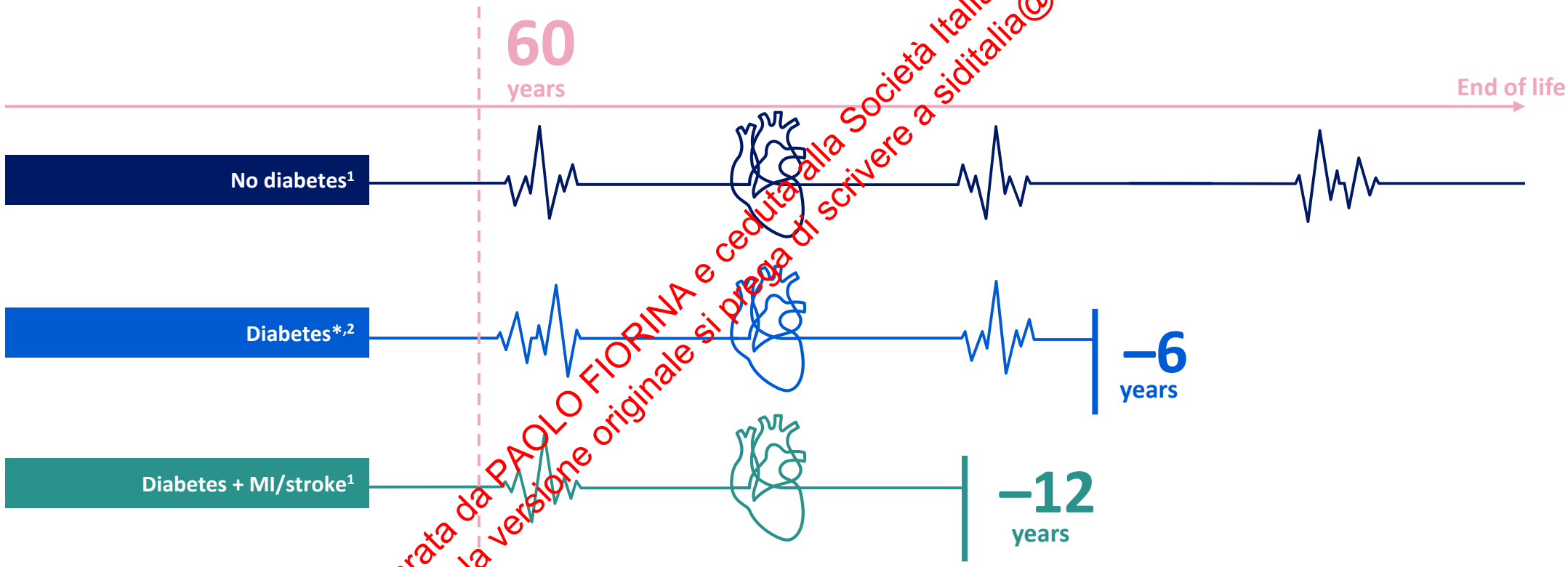
Eur Heart J. 2023

DM is associated with higher cardiovascular mortality



Lee YB et al., Cardiovasc Diabetol 2019

Life expectancy is reduced by 12 years DM+CVD

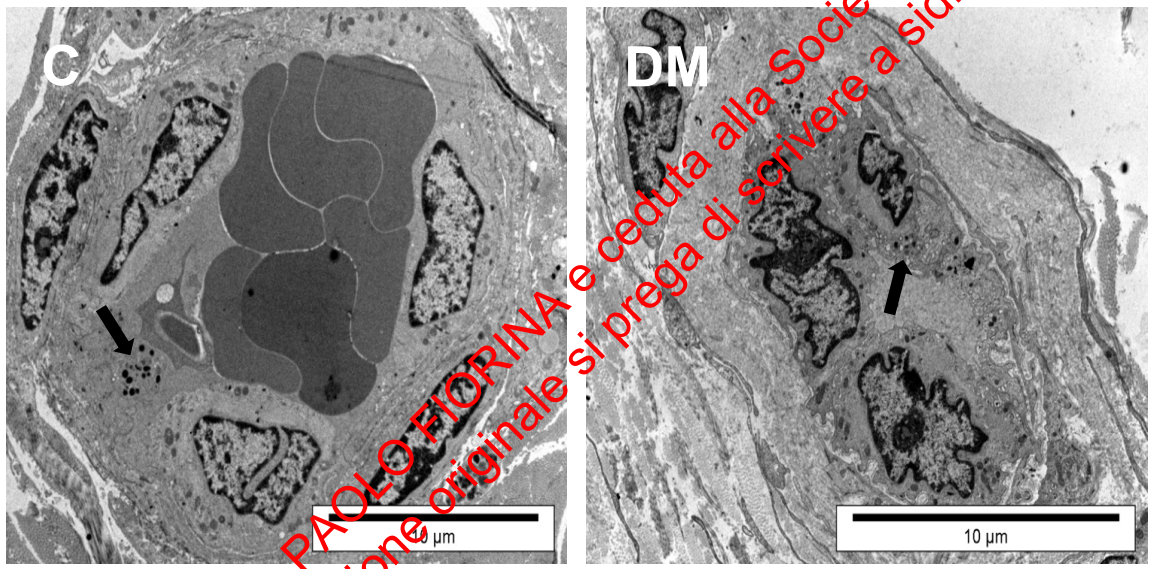


Early screening and further management of cardiovascular risk among younger and newly diagnosed people with T2D is required to protect them from the risk of stroke

Di Angelantonio E et al., JAMA 2015
Sattar N et al., Circulation 2019

Accelerated Atherosclerosis

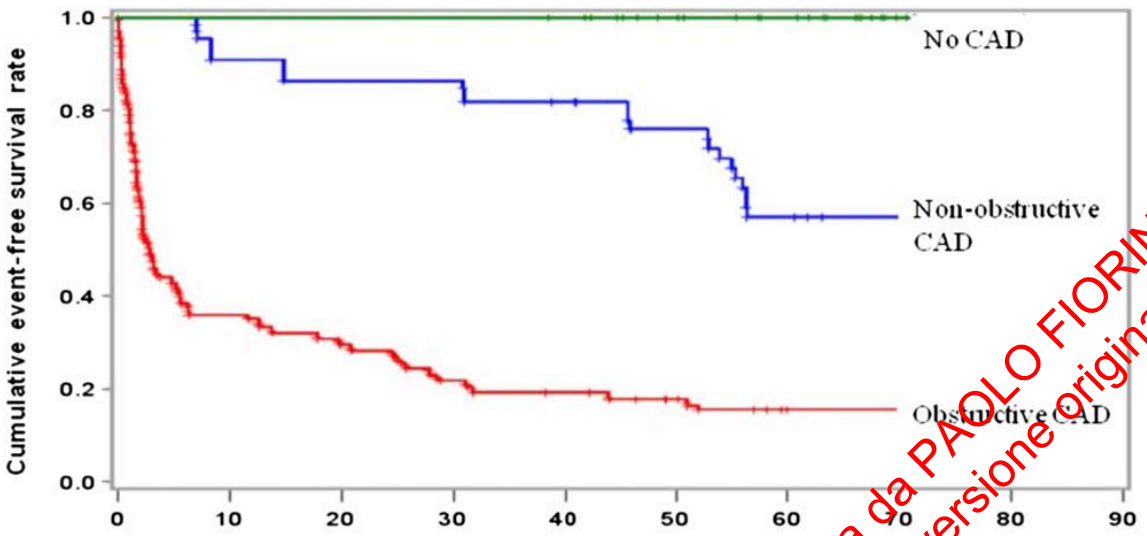
The basis for CVD in DM



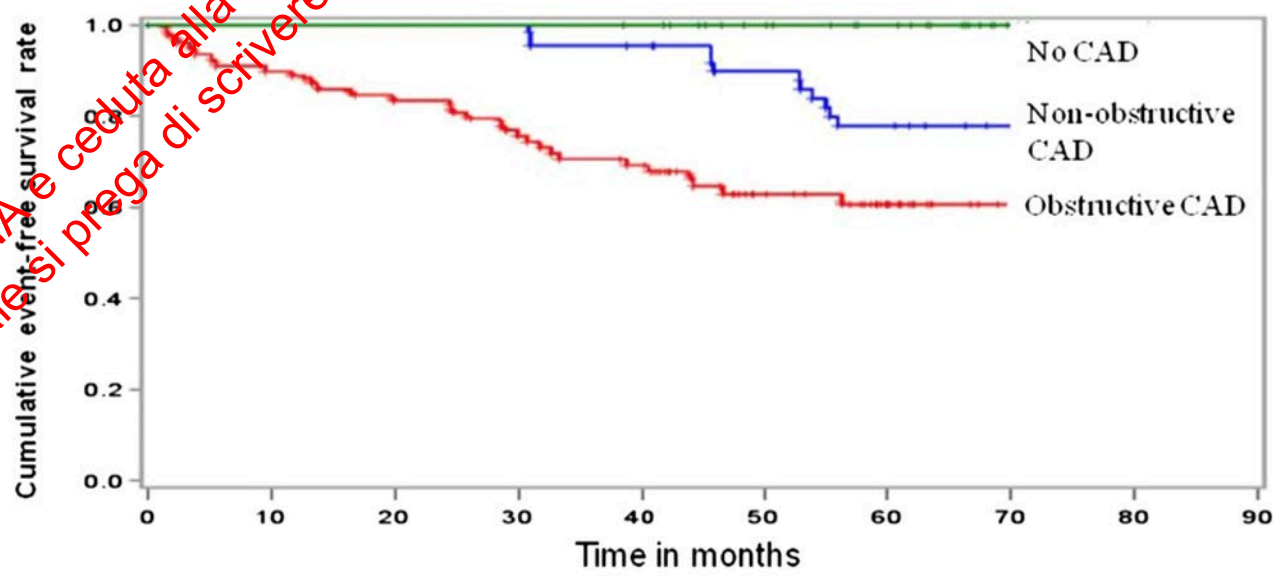
Fiorina P/Folli F et al., Plos One 2011

CAD is the major cause of mortality in patients with DM

All events



Hard events

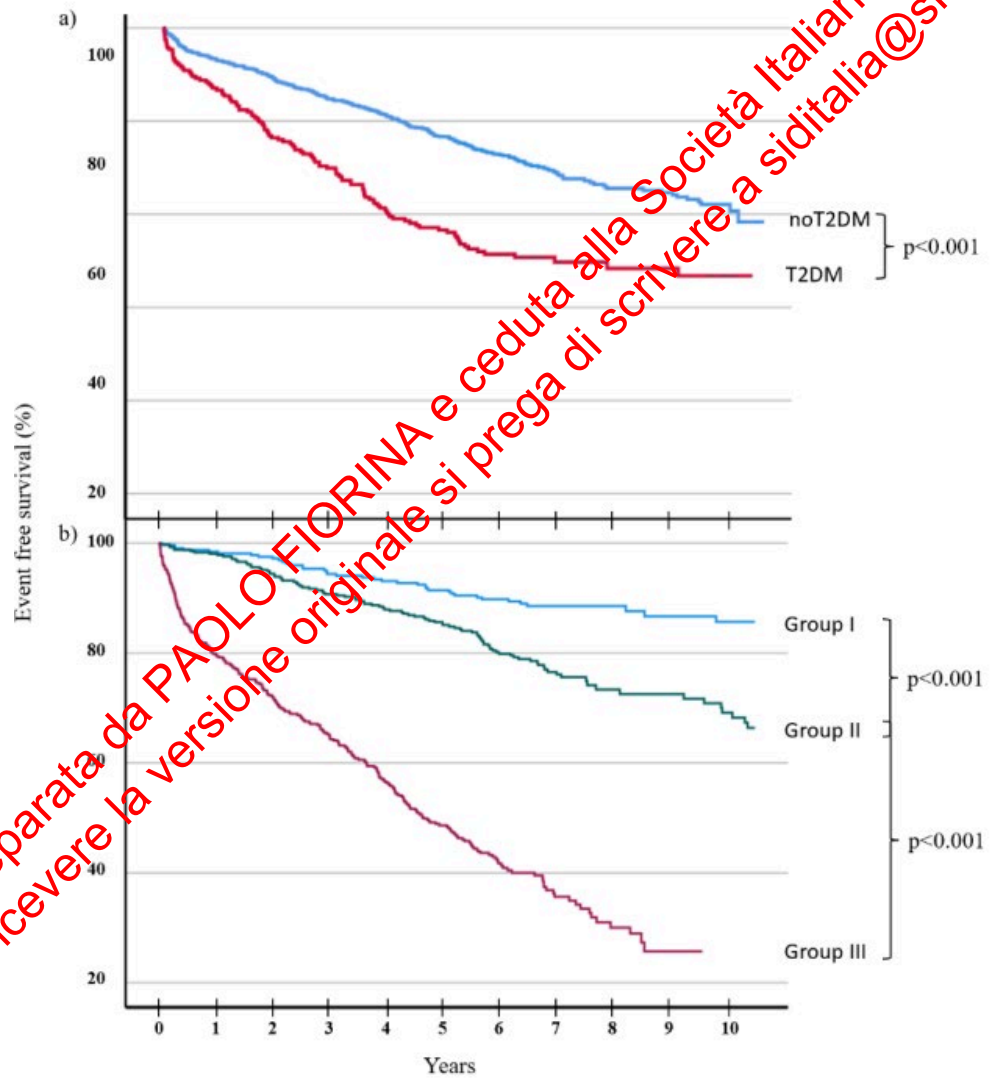


Andreini D et al., Diabetes Care 2013

Incidence of MACE

According to diabetes-state

According to the atherosclerotic grade (Group I-Group III)



Mader A et al., Scientific Reports 2025

Diabetic cardiomyopathy/HFpEF

HF high prevalence in DM

68% who had T2D for 5 years (n=386) showed signs of asymptomatic LV dysfunction

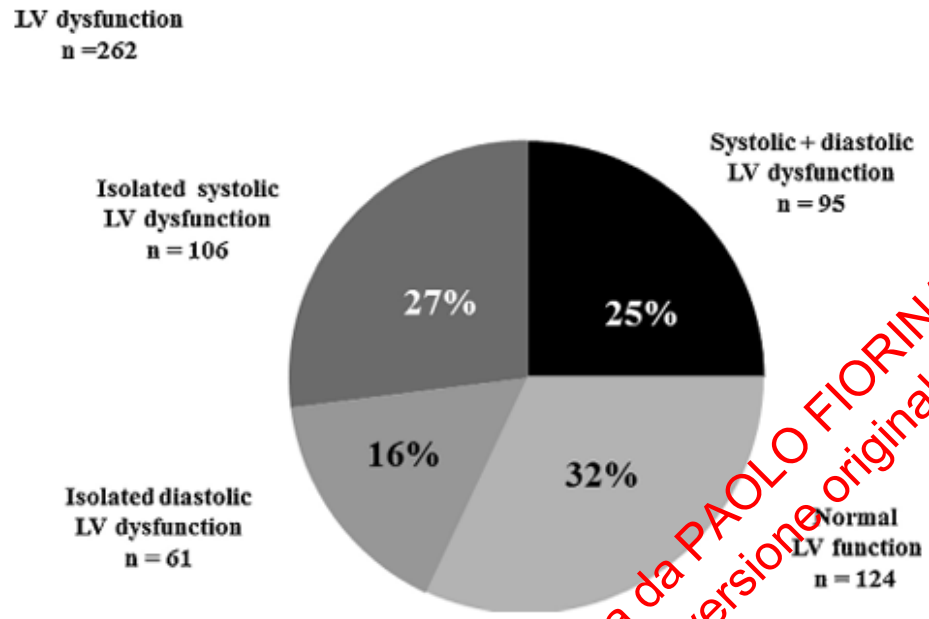


Fig. 1 – Distribution of asymptomatic left ventricular systolic and/or diastolic dysfunction in the SHORTWAVE study population (386 patients).

Left ventricular function in insulin-dependent and in non-insulin-dependent diabetic patients: radionuclide assessment

Astorri E, Fiorina P et al., Cardiology 1997

Isolated and Preclinical Impairment of Left Ventricular Filling in Insulin-Dependent and Non-Insulin-Dependent Diabetic Patients

Astorri E, Fiorina P et al., Clin Card 1997

Faden G et al., Diabetes Res Clin Pract 2013
Boonman-de Winter LJ et al., Diabetologia 2012

Diastolic dysfunction

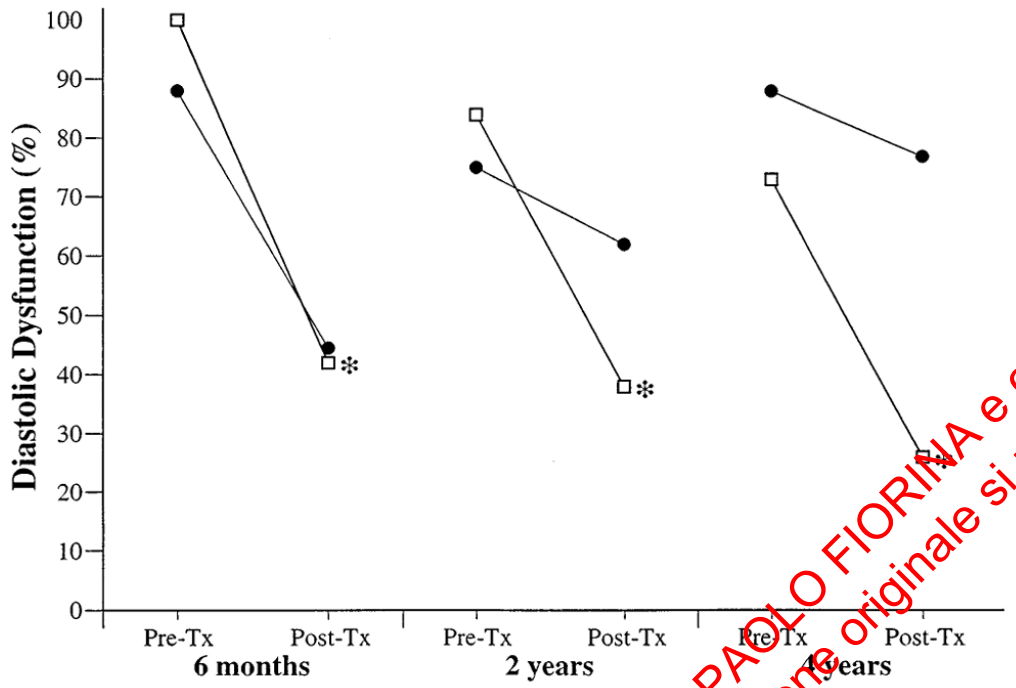


Figure 3—*Rate of diastolic dysfunction pretransplantation (Pre-Tx) and posttransplantation (Post-Tx) in type 1 diabetic patients submitted to kidney-pancreas (□) and kidney alone (■) transplantation. *P < 0.05, posttransplantation vs. pretransplantation.*

Reversal of Left Ventricular Diastolic Dysfunction After Kidney-Pancreas Transplantation in Type 1 Diabetic Uremic Patients

Fiorina P et al., Diabetes Care 2000

Fiorina P et al., Diabetes Care 2000

Glycometabolic control

Poorly controlled DM leads to ⬆ complications

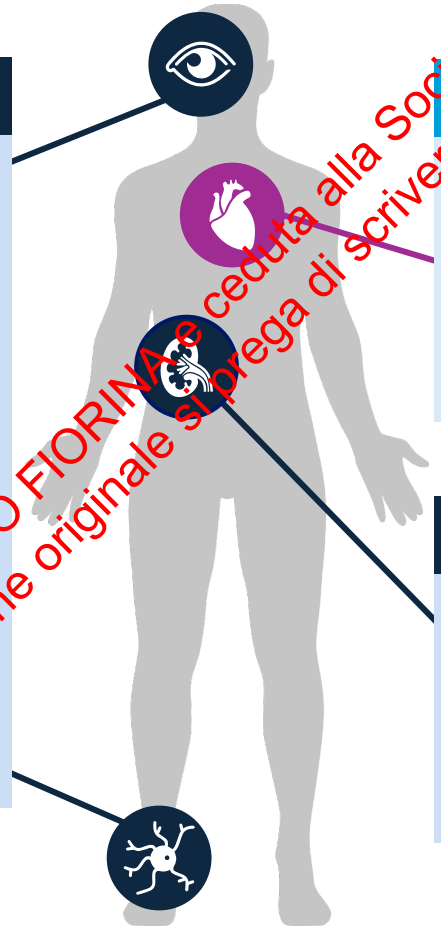
Microvascular

Diabetic retinopathy

- Estimated to affect **35%** of all people with diabetes and is **one of the leading** causes of vision loss in the working age population

Diabetic neuropathy

- Nerve damage can lead to ulceration and lower-limb amputations
- **60%** of lower-limb amputations in adults are caused by type 2 diabetes



Macrovascular

Cardiovascular disease

- Includes angina, CAD, MI, stroke, PAD and CHF
- People with diabetes are **two to three times** more likely to have CVD

Microvascular

Diabetic nephropathy

- Diabetes is a **leading** cause of chronic kidney disease and both conditions are interlinked

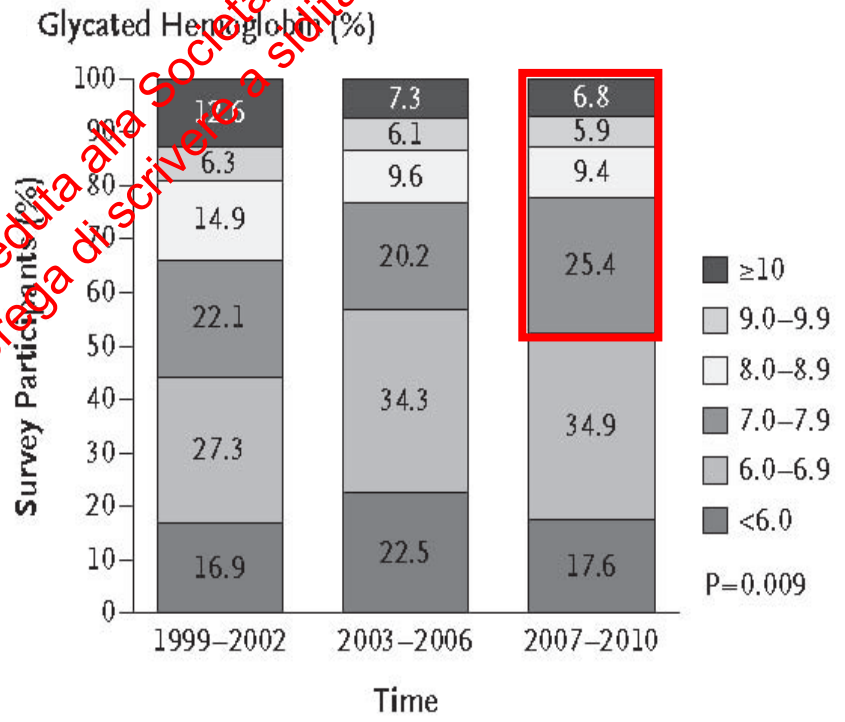
CVD and glycometabolic control

1998-2011 death rate in 34,000 T1D individuals

Mean HbA1c (%)	Death from any cause (HR)	Death from CVD (HR)
≤ 6.9	2.36	2.92
7.0-7.8	2.38	3.39
7.9-8.7	3.11	4.44
8.8-9.7	3.65	5.35
≥ 9.7	**8.51**	**10.46**

Fiorina P et al., WJD 2015
Lind M et al., NEJM 2014

Persisting poor glycemic control in diabetes



Ali MK et al., NEJM 2013

48% have HbA1c ≥7%

Outline

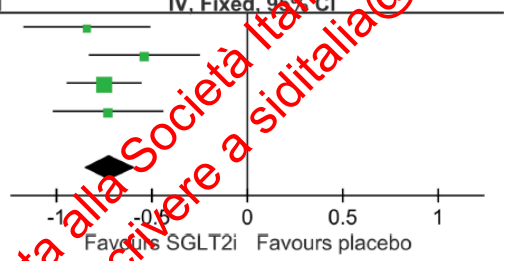
1. Introduction
2. SGLT2i
3. GLP-1RA
4. SGLT2i plus GLP-1RA
5. Conclusions

SGLT2i and glycometabolic control

A HbA1C

	Study or Subgroup	SGLT2i Mean	SGLT2i SD	SGLT2i Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Dapagliflozin 5mg/day	Bailey 2012	-0.82	0.9763	66	0.02	0.9915	68	15.4%	-0.84 [-1.17, -0.51]
Dapagliflozin 5mg/day	Ferrannini 2010	-0.77	0.88	64	-0.23	0.866	75	20.1%	-0.54 [-0.83, -0.25]
Dapagliflozin 5mg/day	Ji 2014	-1.04	0.8004	128	-0.29	0.8131	132	44.3%	-0.75 [-0.95, -0.55]
Remogliflozin 50 mg twice daily	Sykes 2014	-1.04	0.7134	46	-0.31	0.7134	47	20.3%	-0.73 [-1.02, -0.44]
	Total (95% CI)			**304**			**322**	**100.0%**	**-0.72 [-0.85, -0.59]**

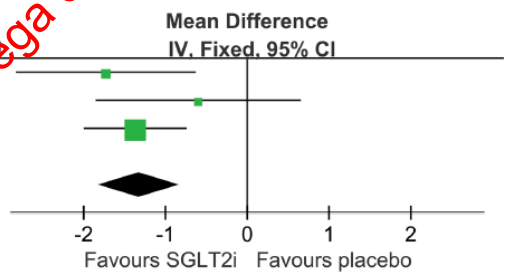
Heterogeneity: Chi² = 2.06, df = 3 (P = 0.56); I² = 0%
Test for overall effect: Z = 10.77 (P < 0.00001)



B Weight

	Study or Subgroup	SGLT2i Mean	SGLT2i SD	SGLT2i Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Dapagliflozin 5mg/day	Bailey 2012	-2.69	3.1978	67	-0.96	3.3227	68	20.8%	-1.73 [-2.83, -0.63]
Dapagliflozin 5mg/day	Ferrannini 2010	-2.8	4	64	-2.2	3.4641	75	16.0%	-0.60 [-1.85, 0.65]
Dapagliflozin 5mg/day	Ji 2014	-1.64	2.5728	128	-0.27	2.6135	132	63.3%	-1.37 [-2.00, -0.74]
	Total (95% CI)			**259**			**275**	**100.0%**	**-1.32 [-1.82, -0.82]**

Heterogeneity: Chi² = 1.82, df = 2 (P = 0.40); I² = 0%
Test for overall effect: Z = 5.17 (P < 0.00001)



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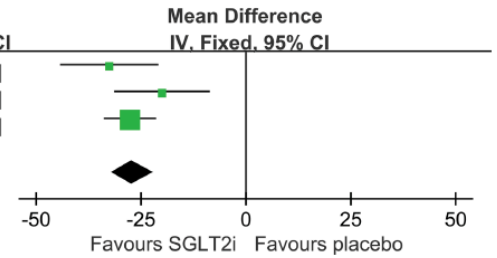
	Study or Subgroup	SGLT2i Mean	SGLT2i SD	SGLT2i Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Dapagliflozin 5mg/day	Bailey 2012	-28.44	33.9457	67	4.14	36.4071	68	17.9%	-32.58 [-44.28, -20.88]
Dapagliflozin 5mg/day	Ferrannini 2010	-24.1	34.4	64	-4	33.776	75	19.0%	-20.00 [-31.38, -8.62]
Dapagliflozin 5mg/day	Ji 2014	-25.1	25.7283	128	2.5	25.5541	132	63.1%	-27.60 [-33.83, -21.37]
	Total (95% CI)			**259**			**275**	**100.0%**	**-27.05 [-32.01, -22.10]**

Heterogeneity: Chi² = 2.36, df = 2 (P = 0.31); I² = 15%
Test for overall effect: Z = 10.70 (P < 0.00001)

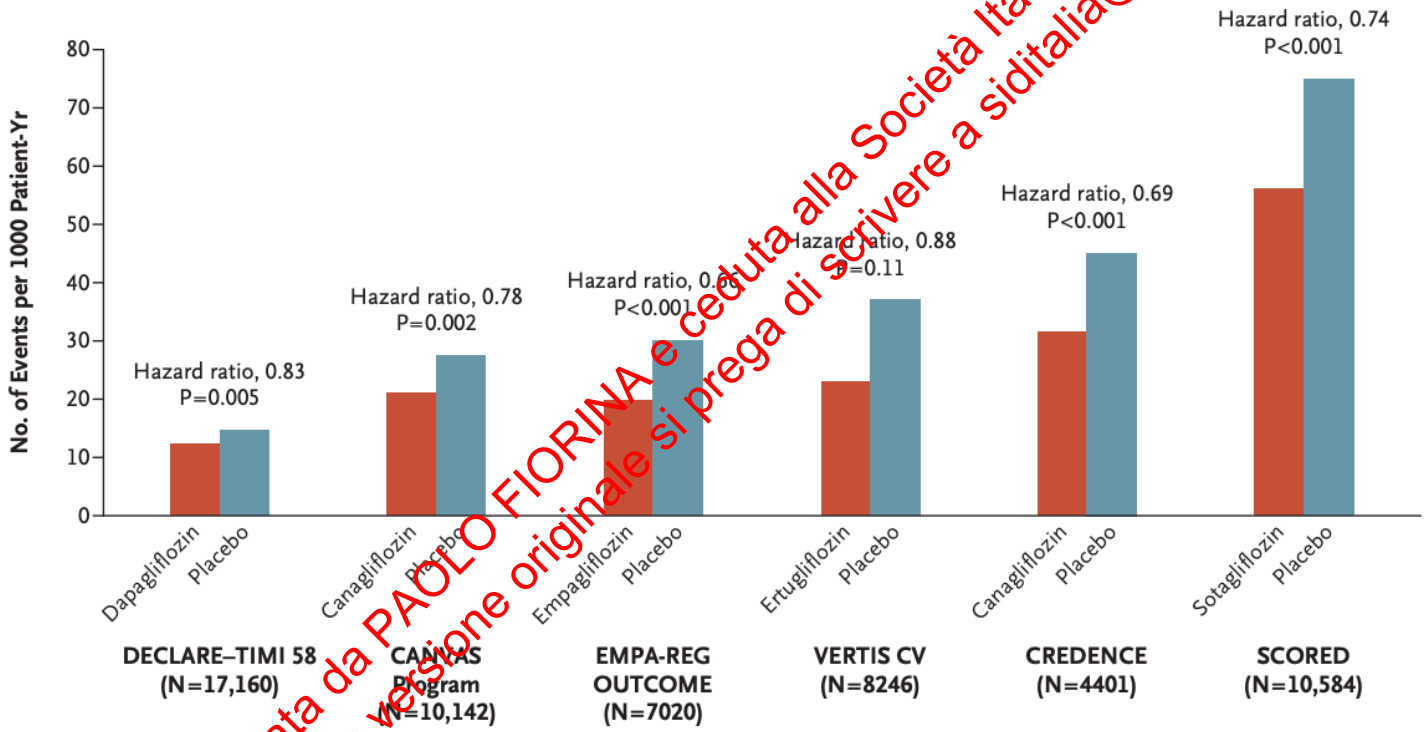


2 SGLT2i VS Placebo

	MD	95%CI	I^2	GRADE
Efficacy				
HbA1c	-0.72	-0.85~-0.59	0%	Moderate
Body weight	-1.32	-1.82~-0.82	0%	Moderate
FPG	-27.05	-32.01~-22.10	15%	High
Side effect	*OR*	*95%CI*	I^2	*GRADE*
Nasopharyngitis	1.07	0.47~2.42	0%	Moderate
UTI	2.31	1.00~5.34	0%	Moderate
Diarrhea	1.18	0.58~2.39	0%	Moderate
Hyperglycemia	1.06	0.36~3.07	0%	Moderate

Deng R et al., Frontiers in Endocrinology 2013

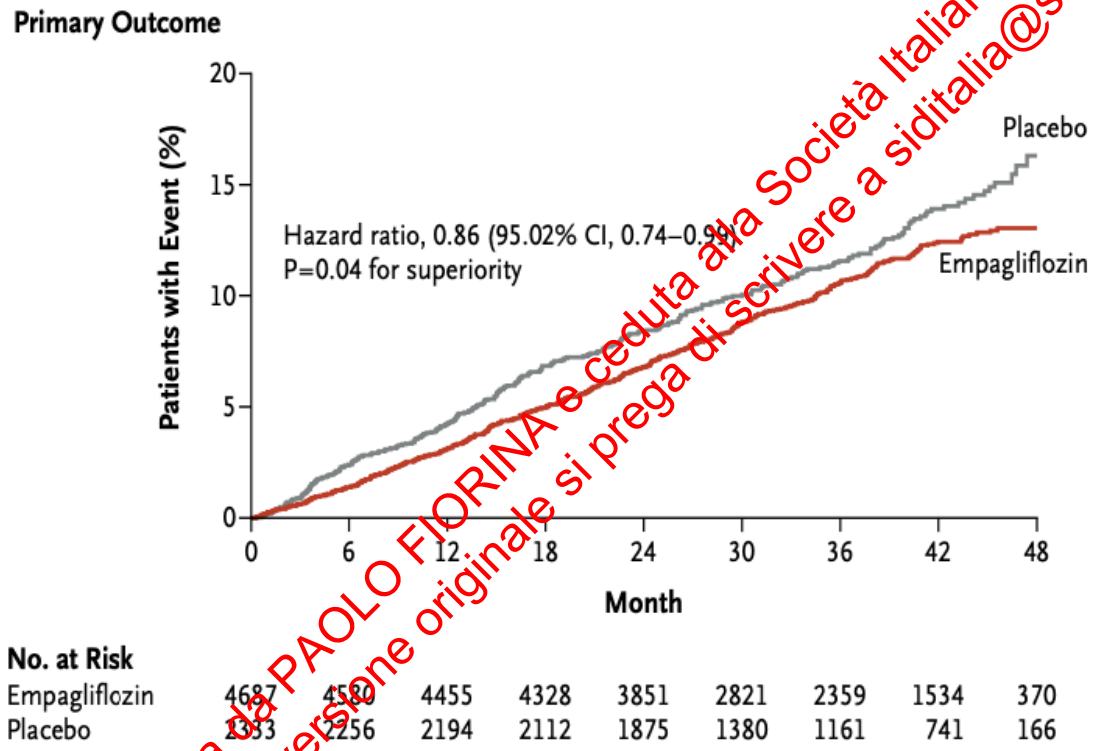
SGLT2i and CVD



Cardiovascular death or hospitalization for HF among patients with T2D

Braunwald E et al., NEJM 2022

Empa and CVD

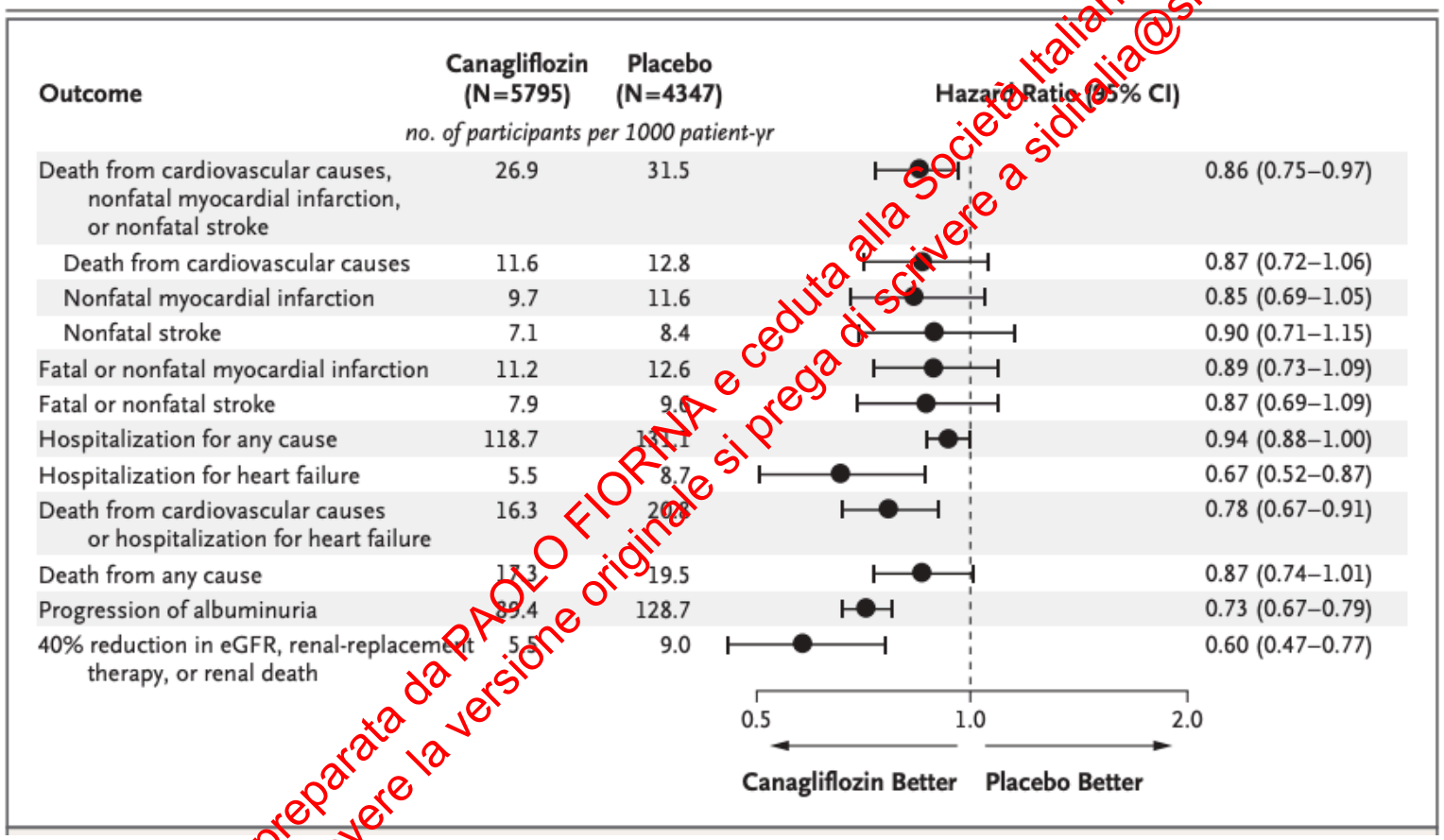


Primary Outcome:
death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke

Zinman B et al., NEJM 2015

Cana and CVD

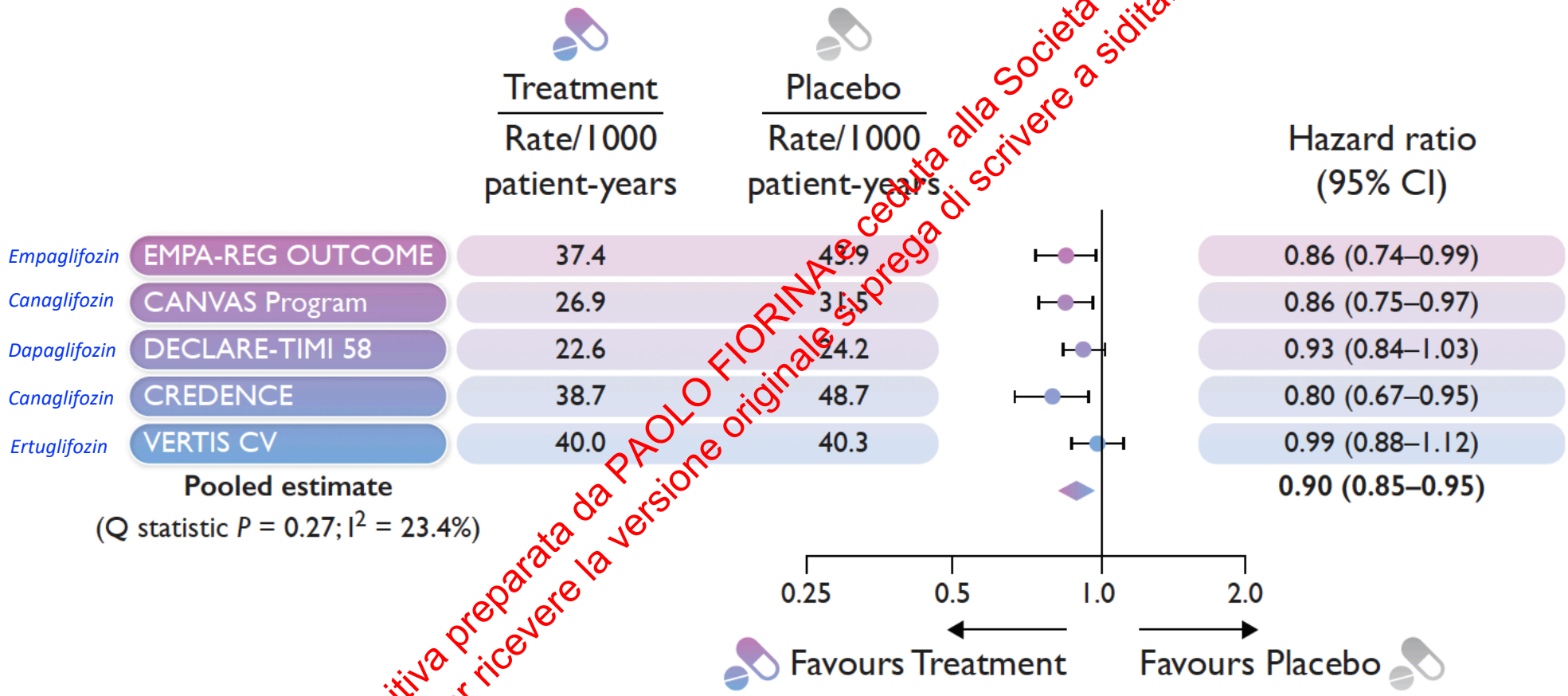
Outcome	Canagliflozin (N=5795)	Placebo (N=4347)	Hazard Ratio (95% CI)
	no. of participants per 1000 patient-yr		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	26.9	31.5	0.86 (0.75–0.97)
Death from cardiovascular causes	11.6	12.8	0.87 (0.72–1.06)
Nonfatal myocardial infarction	9.7	11.6	0.85 (0.69–1.05)
Nonfatal stroke	7.1	8.4	0.90 (0.71–1.15)
Fatal or nonfatal myocardial infarction	11.2	12.6	0.89 (0.73–1.09)
Fatal or nonfatal stroke	7.9	9.6	0.87 (0.69–1.09)
Hospitalization for any cause	118.7	131.1	0.94 (0.88–1.00)
Hospitalization for heart failure	5.5	8.7	0.67 (0.52–0.87)
Death from cardiovascular causes or hospitalization for heart failure	16.3	20.8	0.78 (0.67–0.91)
Death from any cause	17.3	19.5	0.87 (0.74–1.01)
Progression of albuminuria	89.4	128.7	0.73 (0.67–0.79)
40% reduction in eGFR, renal-replacement therapy, or renal death	5.5	9.0	0.60 (0.47–0.77)



Neal B et al., NEJM 2017

SGLT2i and CVD

SGLT2-inhibitors in Patients at High Risk or with ASCVD



McGuire DK et al., JAMA Cardiology 2021

Outline

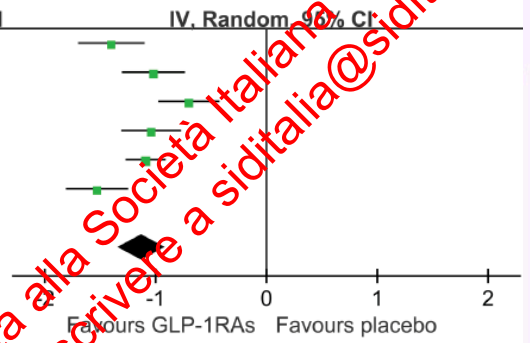
1. Introduction
2. SGLT2i
3. GLP-1RA
4. Combination therapy
5. Conclusions

GLP-1RA and glycometabolic control

A HbA1C

	Study or Subgroup	GLP-1RAs Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Semaglutide 14mg/day	Aroda 2019	-1.5	1.4379	175	-0.1	1.4379	178	15.6%	-1.40 [-1.70, -1.10]
Exenatide 200mg once weekly	Ji 2021	-1.41	0.7941	63	-0.39	0.8269	62	16.1%	-1.02 [-1.30, -0.74]
Exenatide 10ug twice a day	Moretto 2008	-0.9	0.8832	78	-0.2	0.8775	77	16.3%	-0.70 [-0.98, -0.42]
Albiglutide 50 mg once a week	Nauck 2016	-0.89	0.9553	97	0.15	0.9651	99	16.6%	-1.04 [-1.31, -0.77]
Taspoglutide 20mg once a week	Raz 2012	-1.18	0.6762	127	-0.09	0.7507	115	19.2%	-1.09 [-1.27, -0.91]
Semaglutide 1 mg once a week	Sorli 2017	-1.55	1.0949	130	-0.02	1.2054	129	16.2%	-1.53 [-1.81, -1.25]
	Total (95% CI)			**670**			**660**	**100.0%**	**-1.13 [-1.35, -0.91]**

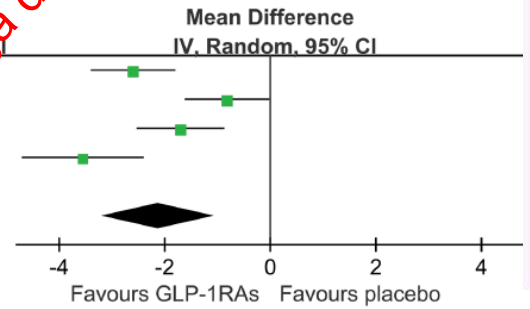
Heterogeneity: Tau² = 0.06; Chi² = 21.29, df = 5 (P = 0.0007); I² = 77%
Test for overall effect: Z = 10.09 (P < 0.00001)



B Weight

	Study or Subgroup	GLP-1RAs Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Semaglutide 14mg/day	Aroda 2019	-4.1	3.8343	175	-1.5	3.8343	178	26.0%	-2.60 [-3.40, -1.80]
Semaglutide 14mg/day	Ji 2021	-1.48	2.2817	63	-0.66	2.2817	62	26.0%	-0.82 [-1.62, -0.02]
Albiglutide 50 mg once a week	Moretto 2008	-3.1	2.6495	78	-1.4	2.6325	77	25.7%	-1.70 [-2.53, -0.87]
Semaglutide 1 mg once a week	Sorli 2017	-4.53	4.6678	130	-0.98	4.8217	129	22.4%	-3.55 [-4.71, -2.39]
	Total (95% CI)			**446**			**446**	**100.0%**	**-2.12 [-3.20, -1.04]**

Heterogeneity: Tau² = 0.99; Chi² = 17.90, df = 3 (P = 0.0005); I² = 83%
Test for overall effect: Z = 3.86 (P = 0.0001)



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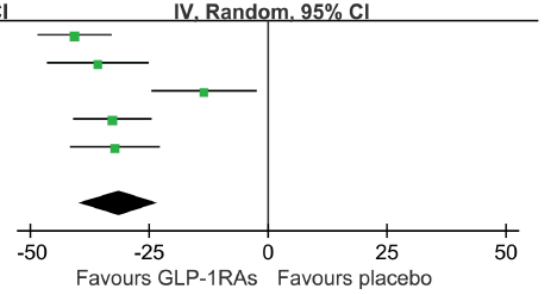
	Study or Subgroup	GLP-1RAs Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Semaglutide 14mg/day	Aroda 2019	-36.7	37.3842	175	[illegible]	37.3842	178	21.8%	-40.70 [-48.50, -32.90]
Semaglutide 14mg/day	Ji 2021	-39.96	30.733	63	[illegible]14	30.4781	62	18.6%	-35.82 [-46.55, -25.09]
Albiglutide 50 mg once a week	Moretto 2008	-18.7	35.327	78	-5.2	35.0999	77	18.2%	-13.50 [-24.59, -2.41]
Taspoglutide 20mg once a week	Raz 2012	-34.2	32.456	127	-1.44	32.8148	115	21.3%	-32.76 [-41.00, -24.52]
Semaglutide 1 mg once a week	Sorli 2017	-42.12	37.3427	130	-9.9	40.2957	129	20.0%	-32.22 [-41.68, -22.76]
	Total (95% CI)			**573**			**561**	**100.0%**	**-31.44 [-39.76, -23.13]**

Heterogeneity: Tau² = 66.70; Chi² = 15.90, df = 4 (P = 0.003); I² = 75%
Test for overall effect: Z = 7.41 (P < 0.00001)



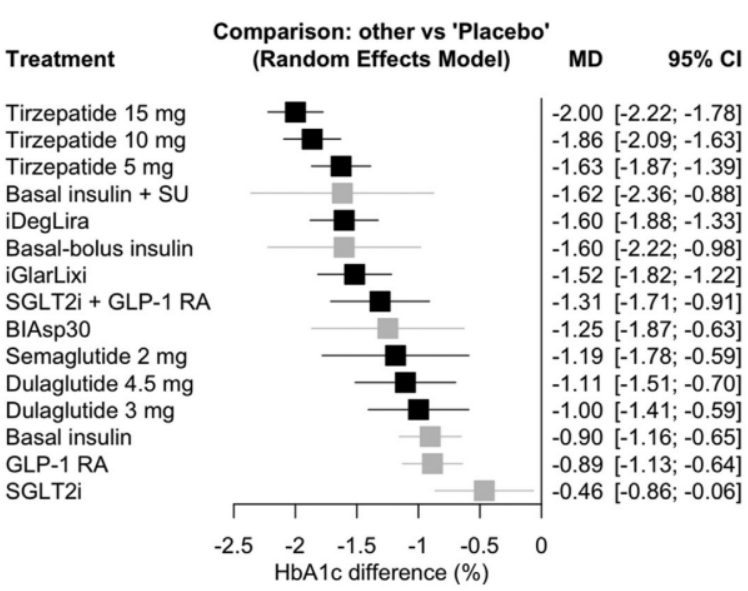
1 GLP-1RAs VS Placebo

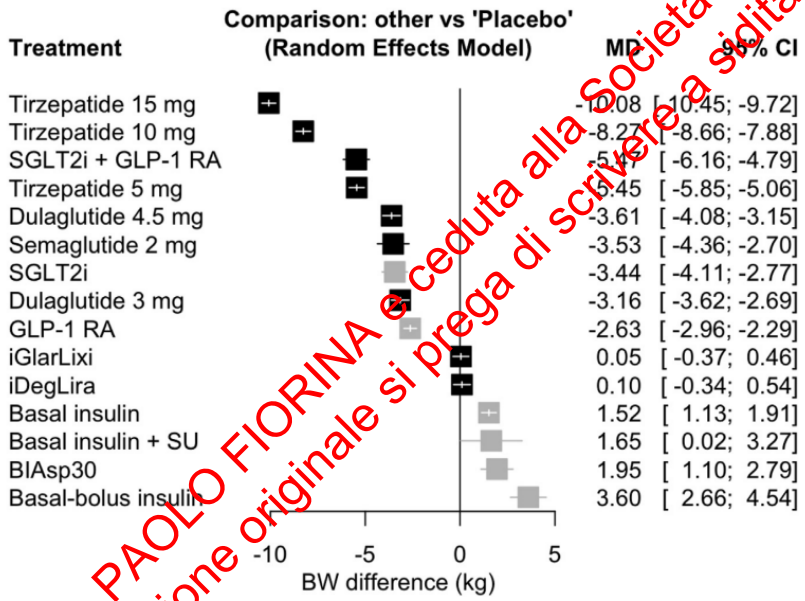
Efficacy	*MD*	*95%CI*	*I²*	*GRADE*
HbA1c	-1.13	-1.35~-0.91	77%	Moderate
Body weight	-2.12	-3.20~-1.04	83%	Moderate
FPG	-31.44	-39.76~-23.13	75%	Moderate

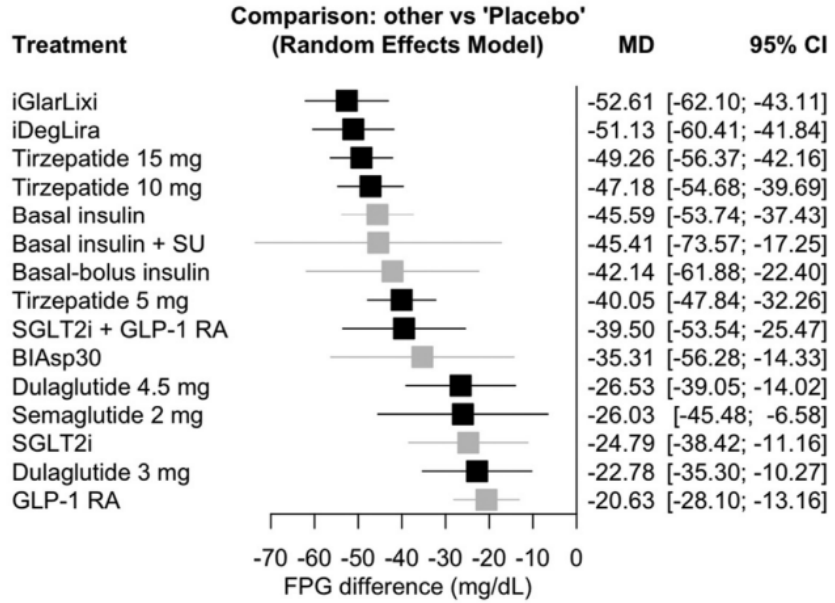
Side effect	*OR*	*95%CI*	*I²*	*GRADE*
Diarrhea	2.18	1.32~3.60	10%	Moderate
Hypoglycemia	3.10	1.34~7.16	0%	Moderate
vomiting	8.22	4.02~16.81	24%	Moderate
Nausea	4.41	2.98~6.55	63%	Low

Deng R et al., Frontiers in Endocrinology 2013

GLP-1RA and glycometabolic control



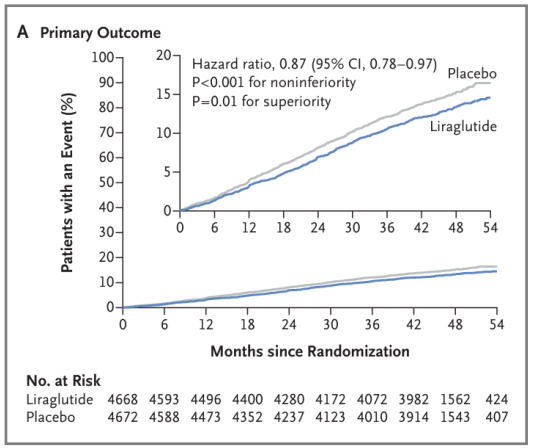




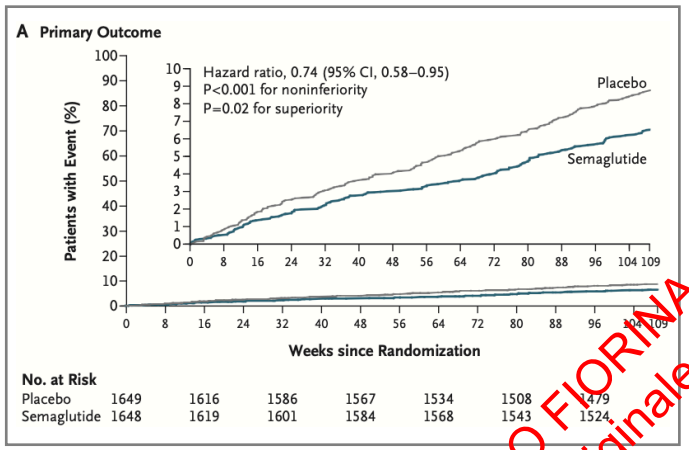
Caruso I et al., Lancet 2023

GLP-1RA and MACE

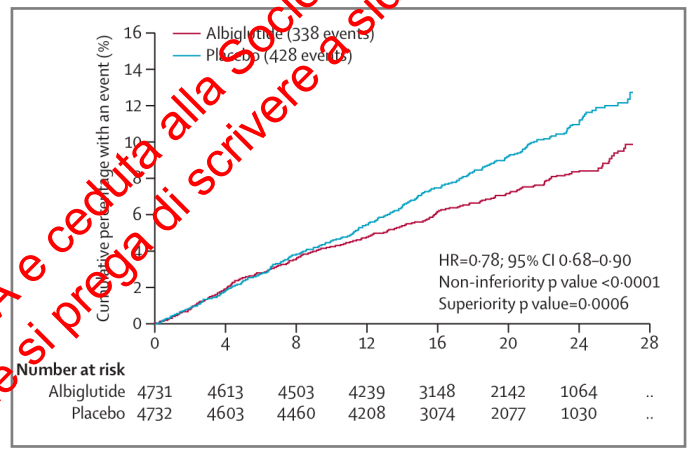
Primary outcome: death from cardiovascular causes, myocardial infarction, or stroke



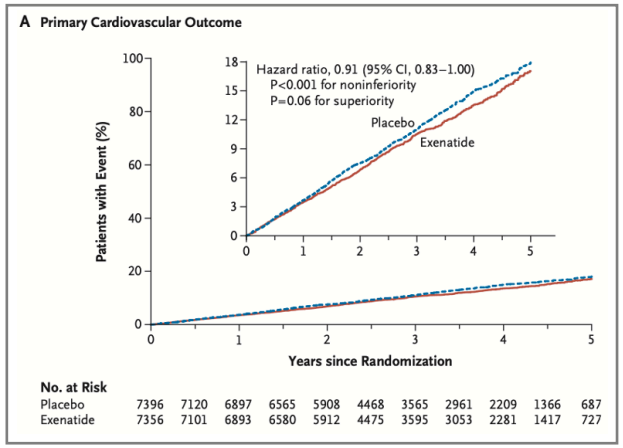
LEADER



SUSTAIN



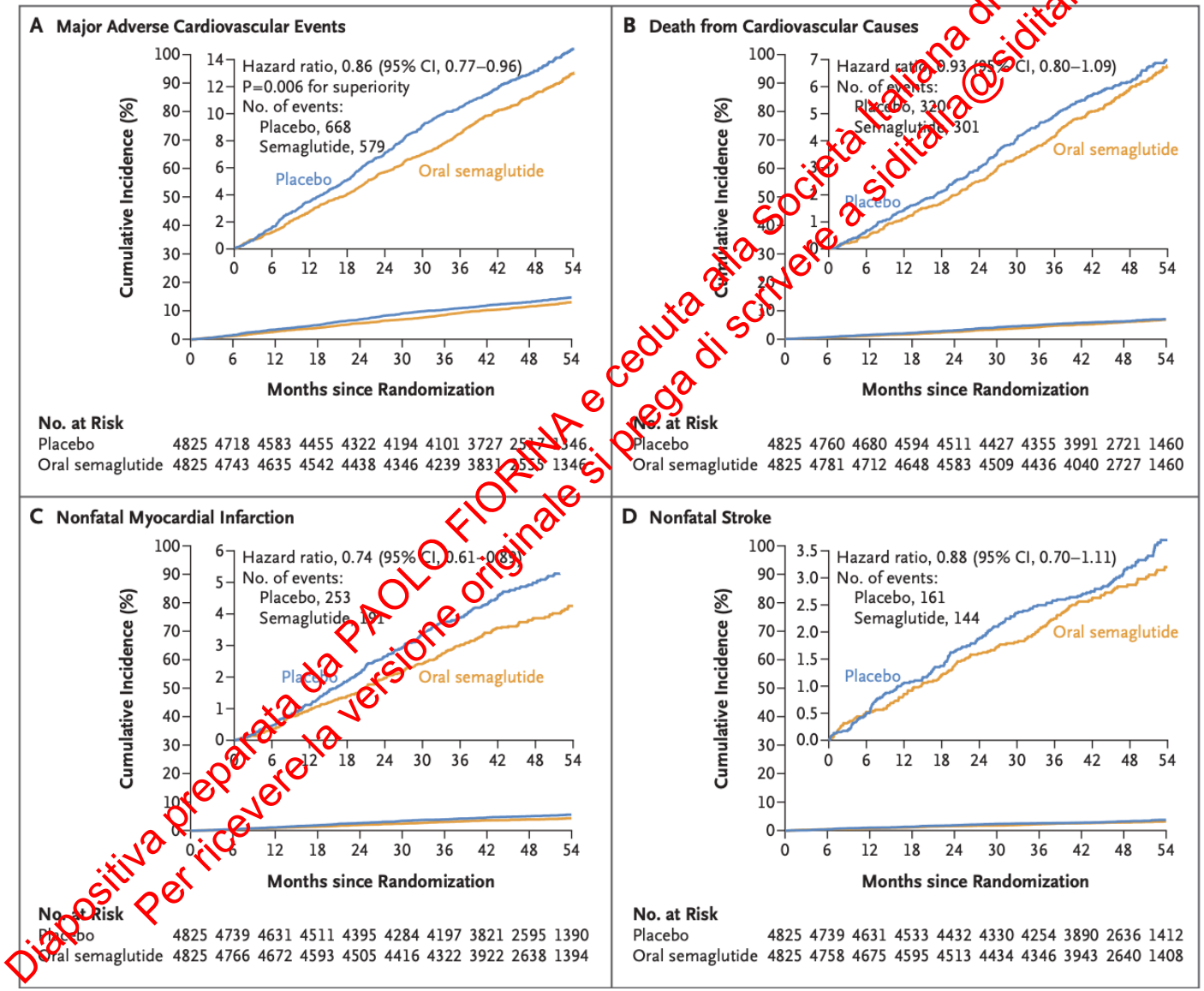
HARMONY OUTCOMES



REWIND

Marso SP et al, NEJM 2016
Hernandez AF et al., The Lancet 2018
Gerstein HC et al., The Lancet, 2019

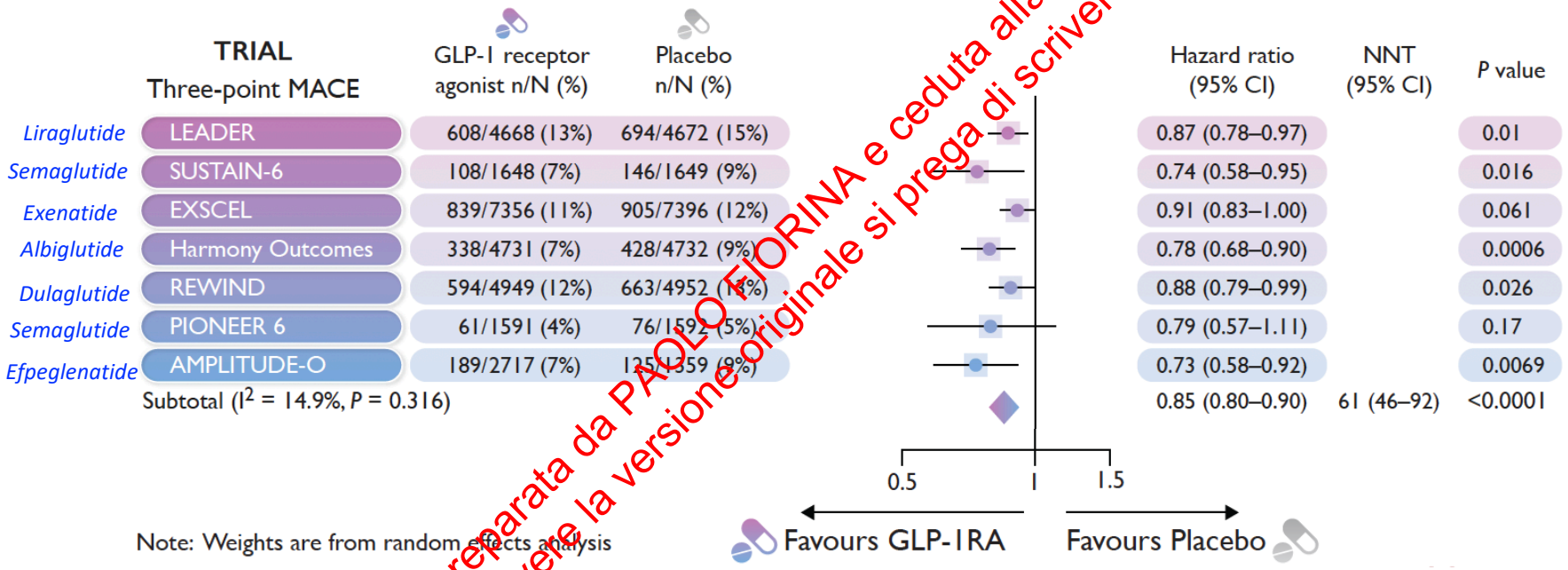
Oral Semaglutide and "The Soul" Study



D.K. McGuire et al., NEJM 2025

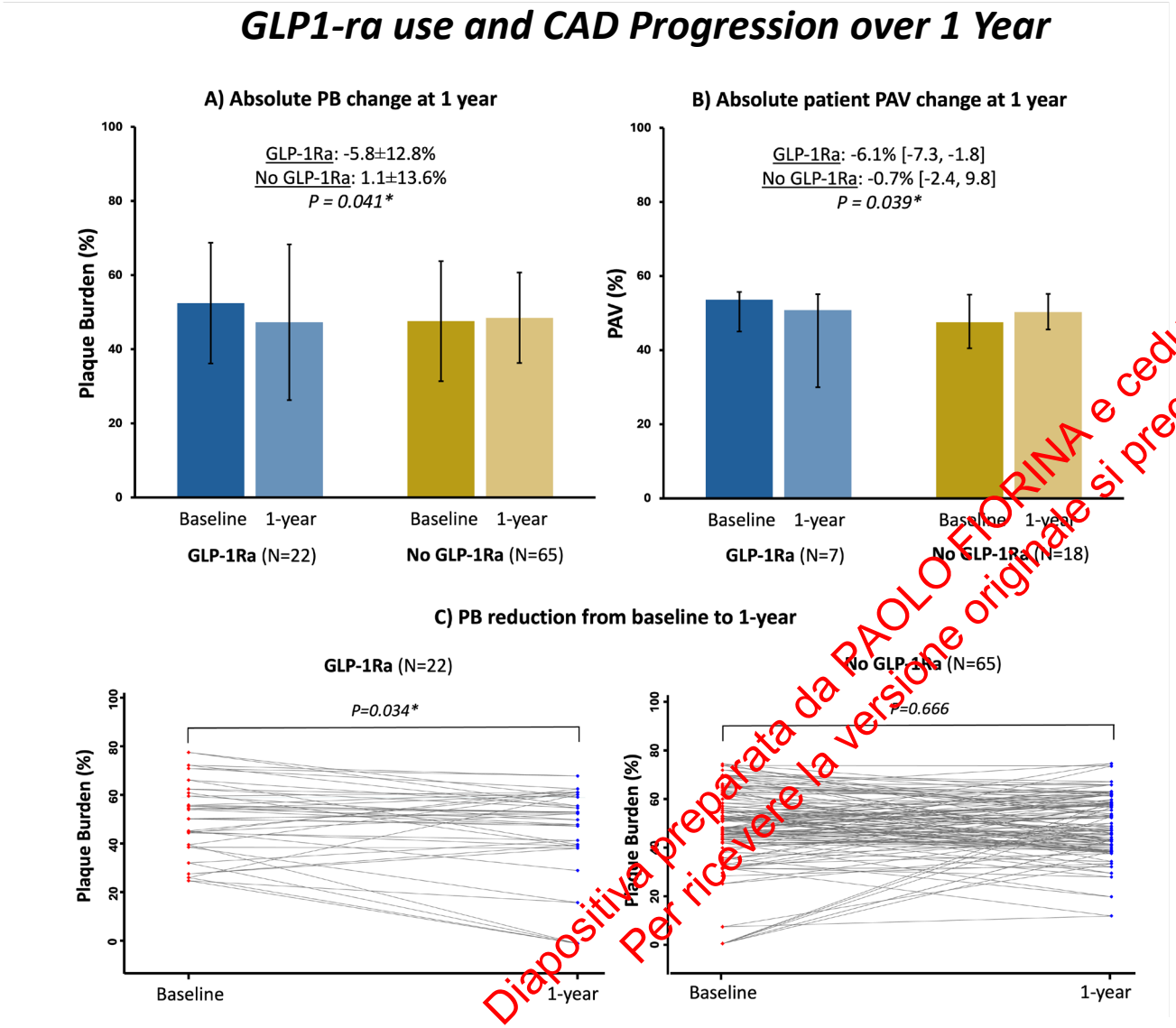
GLP1RA and CVD

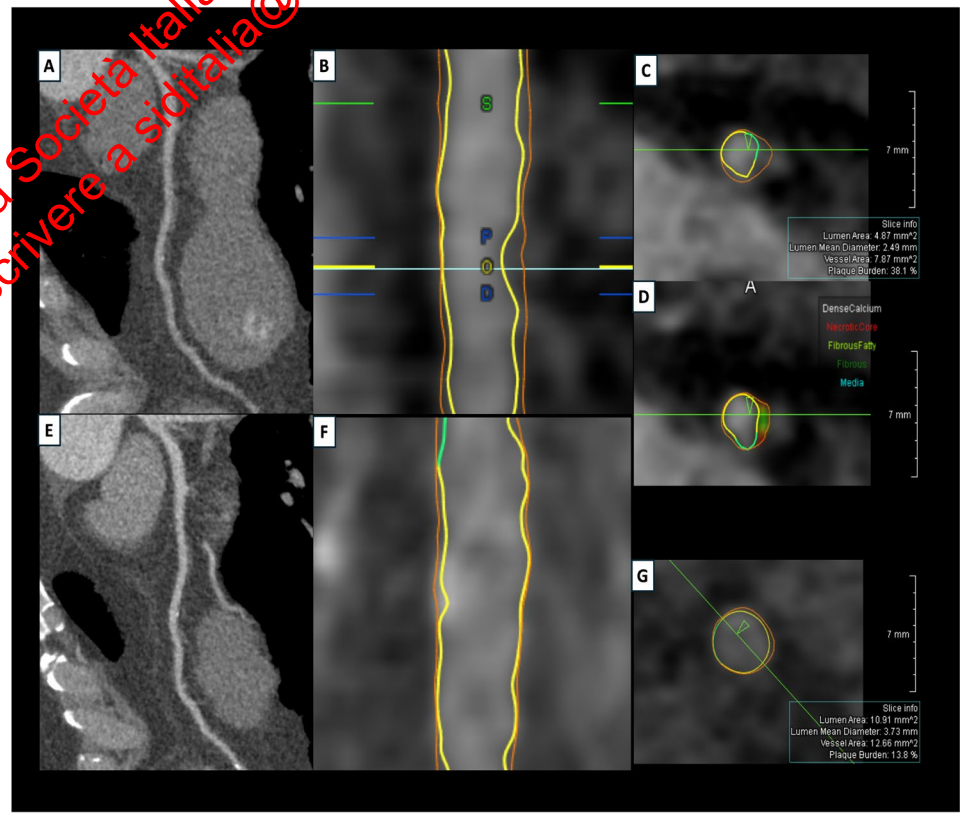
Impact of GLP1-ra on the risk of MACE



Sattar N et al., Lancet 2021

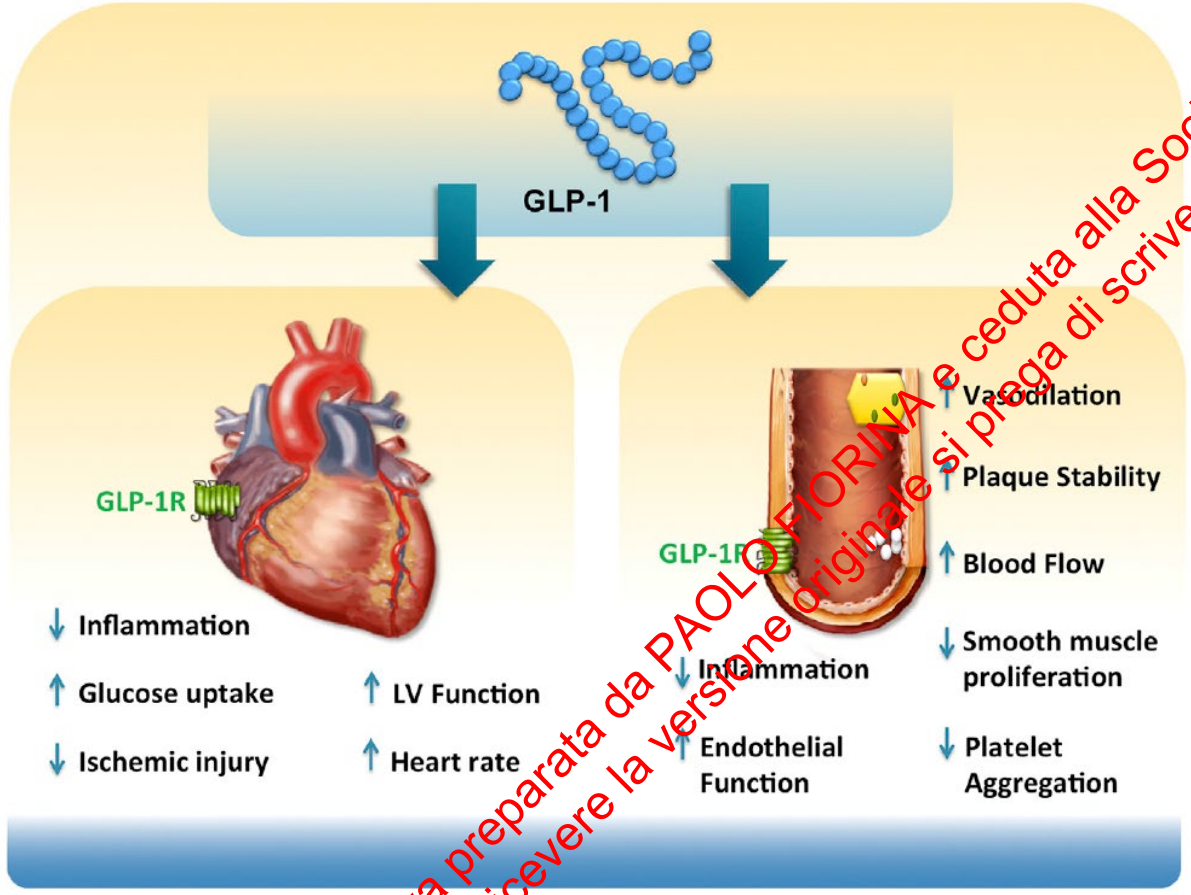
GLP-1RA and coronary plaque regression

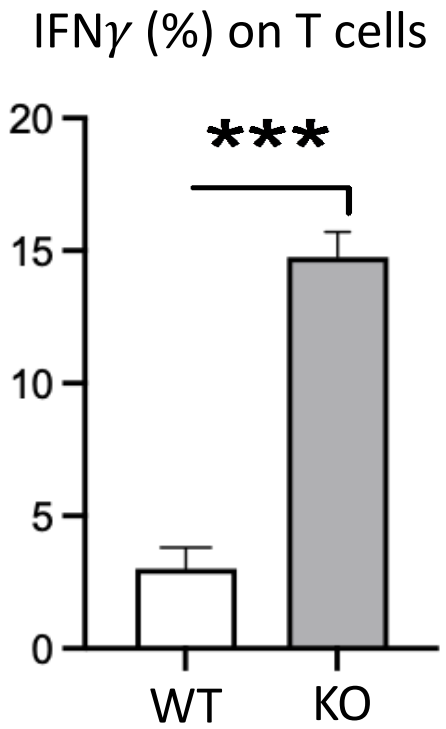




Stefanini G/Fiorina P et al., Under revision

GLP-1RA effects on inflammation





Drucker D. Cell Metabolism 2016
Fiorina et al., Cell Metab 2024

Outline

1. Introduction
2. SGLT2i
3. GLP-1RA
4. Combination therapy
5. Conclusions

Dapa + Oral Sema and DM remission

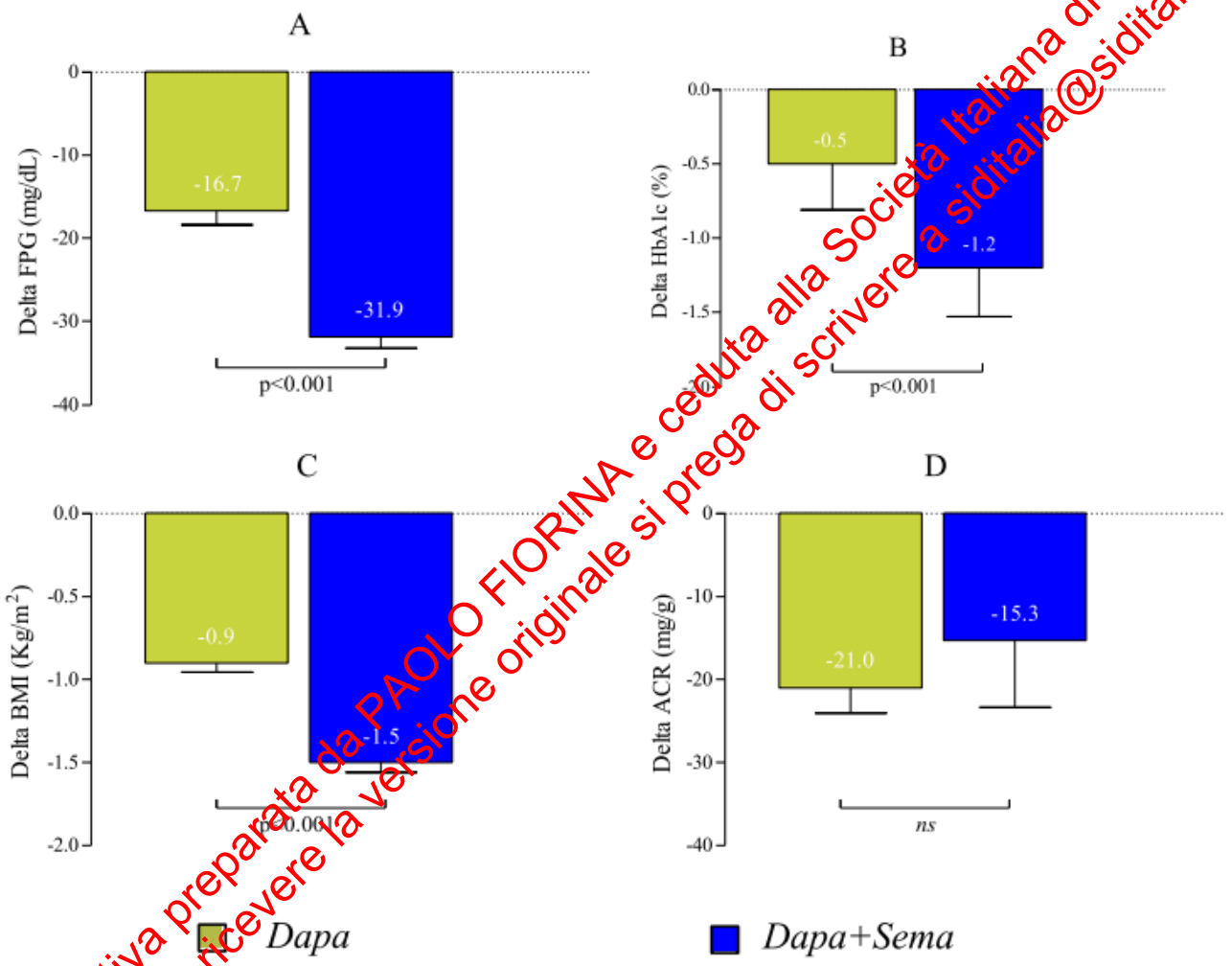
Glycometabolic parameters of patients that completed the 6 months follow-up.

	Dapa (n = 415)				*Dapa+Sema* (n = 544)			
	Basal	Follow up	Mean reduction	*P value*	Basal	Follow-up	Mean reduction	*P value*
BMI (Kg/m^2)	28.4 ± 4.4	27.5 ± 4.4	-0.9	*0.001*	28.6 ± 3.3	27.1 ± 3.0	-1.5	*0.001*
Weight (Kg)	79.6 ± 14.1	77.1 ± 13.9	-2.5	*0.001*	80.4 ± 13.5	76.2 ± 12.1	-4.2	*0.001*
FPG (mg/dL)	152.7 ± 35.8	136 ± 24.6	-16.7	*0.001*	177 ± 30.8	145.1 ± 19.5	-31.9	*0.001*
HbA1c (%)	7.4 ± 0.9	6.9 ± 0.7	-0.5	*0.001*	7.6 ± 0.7	6.4 ± 0.45	-1.2	*0.001*
S-Creatinine (mg/dL)	1.0 ± 0.3	1.1 ± 0.3	+ 0.06	*Ns*	0.94 ± 0.19	0.91 ± 0.17	-0.03	*0.001*
eGFR (mL/min/1,73 m^2)	72.8 ± 23.5	72.4 ± 37.5	-0.4	*Ns*	76.2 ± 24	75.1 ± 20.1	-1.1	*ns*
ACR (mg/g)	52.7 ± 157	31.7 ± 54.9	-21.0	*0.001*	66.2 ± 160	50.9 ± 111	-15.3	*0.01*
Tot-cholesterol (mg/dL)	166.4 ± 37.4	159.7 ± 32.0	-6.7	*0.001*	188 ± 31.7	172.5 ± 19.5	-15.5	*0.001*
HDL (mg/dL)	47.5 ± 12.3	47.8 ± 11.6	+ 0.3	*ns*	42.9 ± 8.4	44.1 ± 7.1	+ 1.2	*0.01*
LDL (mg/dL)	95.0 ± 35.1	84.0 ± 23.2	-6.5	*0.001*	116.4 ± 35.3	97.8 ± 25.3	-18.6	*0.01*
Triglycerides (mg/dL)	145.3 ± 65.1	135.0 ± 53.2	-10.3	*0.000*	142.8 ± 47.3	150.7 ± 29.7	+ 7.9	*0.001*
SBP (mmHg)	134.1 ± 14.7	129.0 ± 12.0	-5.1	*0.000*	133.5 ± 13	123 ± 9,4	-10.5	*0.001*
DBP (mmHg)	80.1 ± 9.0	77.0 ± 8.4	-3.1	*ns*	80.7 ± 8.8	73.3 ± 8.3	-7.4	*0.001*
Basal Insulin treatment	68, 16.4	53, 12.7	-22	*0.001*	120, 22.1	13, 2.4	-89.2	*0.001*
Rapid Insulin treatment	37, 8.9	25, 6.0	-32.4	*0.001*	5, 0.9	0, 0.0	-100	*0.001*
Sulfonylureas/glinides treatment	38, 9.1	7, 1.6	-81.6	*0.014*	55, 1.0	1, 0.2	-98.2	*0.001*

Abbreviations: BMI, body mass index; FPG, Fasting Plasma Glucose; HbA1c, glycated hemoglobin; eGFR Estimated Glomerular Filtration Rate; ACR, albumin/creatinine ratio; HDL high density lipoprotein; LDL low density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure. T-test for repeated measures. Data are expressed as mean ± SD; n, %.

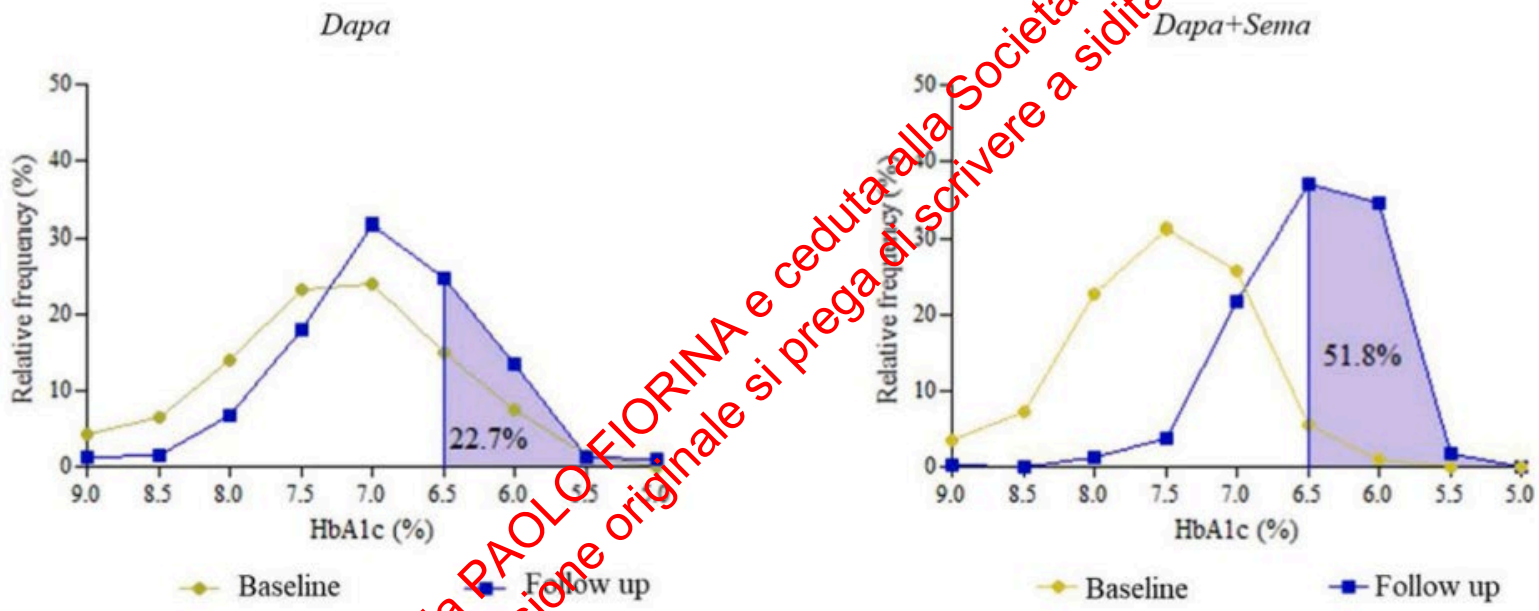
Fiorina P et al., Pharmacological Research 2024

Improvement in all metabolic parameters



Fiorina P et al., Pharmacological Research 2024

Pharmacological remission with GLP-1Ra + SGLT2i



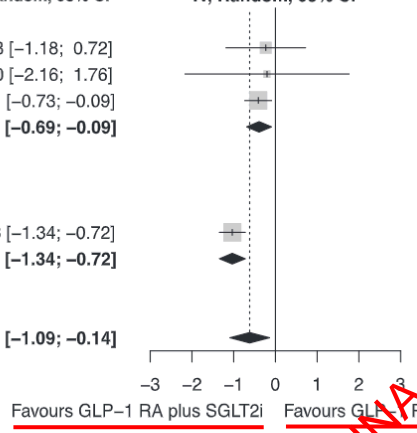
Fiorina P et al., Pharmacological Research 2024

SGLT2i+GLP-1Ra is superior for HbA1c/Body Weight

HbA1c

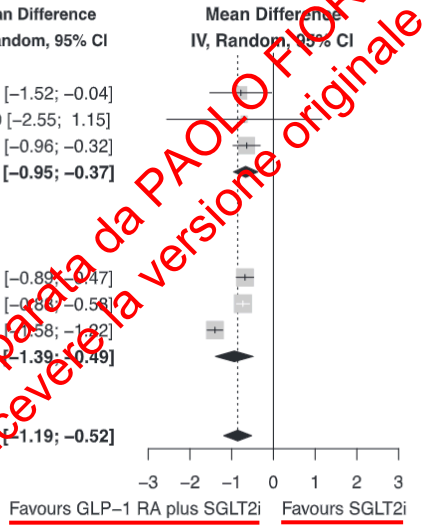
(A)

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)

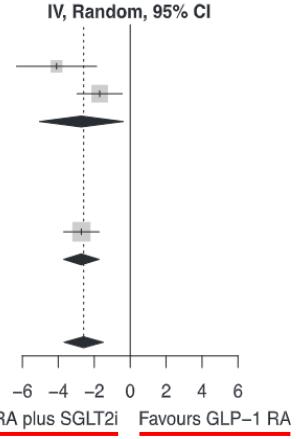
Study or Subgroup	GLP–1 RA plus SGLT2i Mean	SD	Total	SGLT2i Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Simultaneous initiation of GLP–1 RA plus SGLT2i								
Ali 2020[36]	−1.67	1.12	15	−0.89	0.93	15	11.0%	−0.78 [−1.52; −0.04]
Ikonomidis 2018[28]	−1.50	3.58	20	−0.80	2.24	20	2.9%	−0.70 [−2.55; 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 [−0.86; −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%**	**−0.86 [−1.19; −0.52]**
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 41.09$, df = 5 ($P < 0.01$); $I^2 = 88\%$								



Body Weight

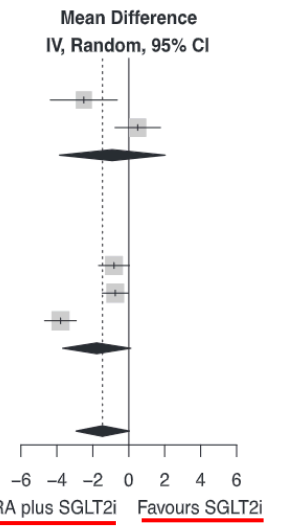
(A)

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 ($P = 0.15$); $I^2 = 47\%$								



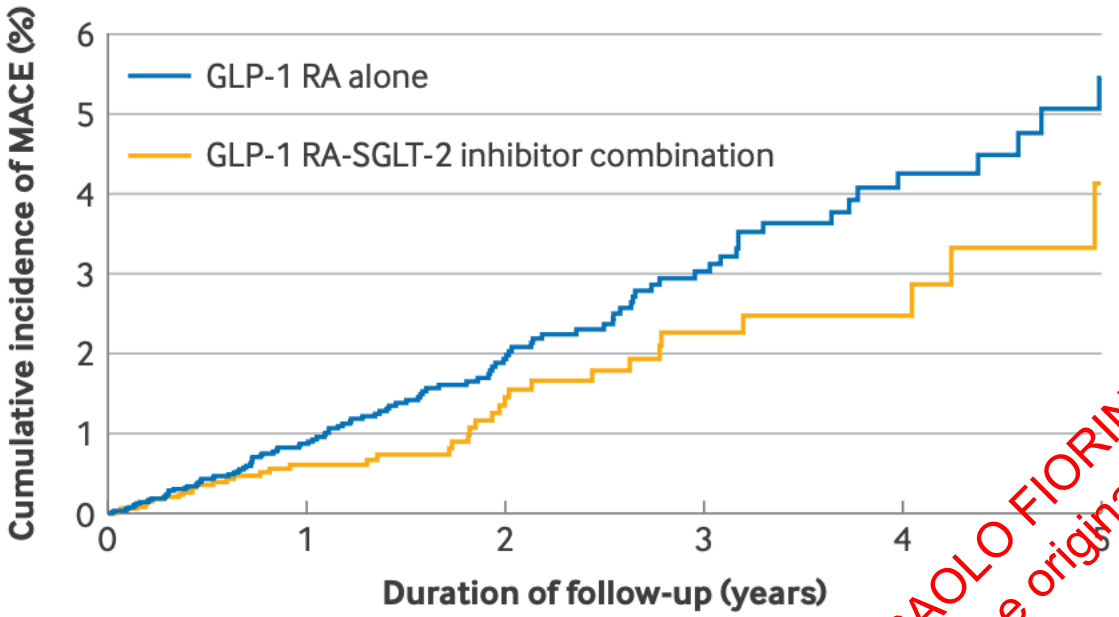
(B)

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 ($P < 0.01$); $I^2 = 91\%$								



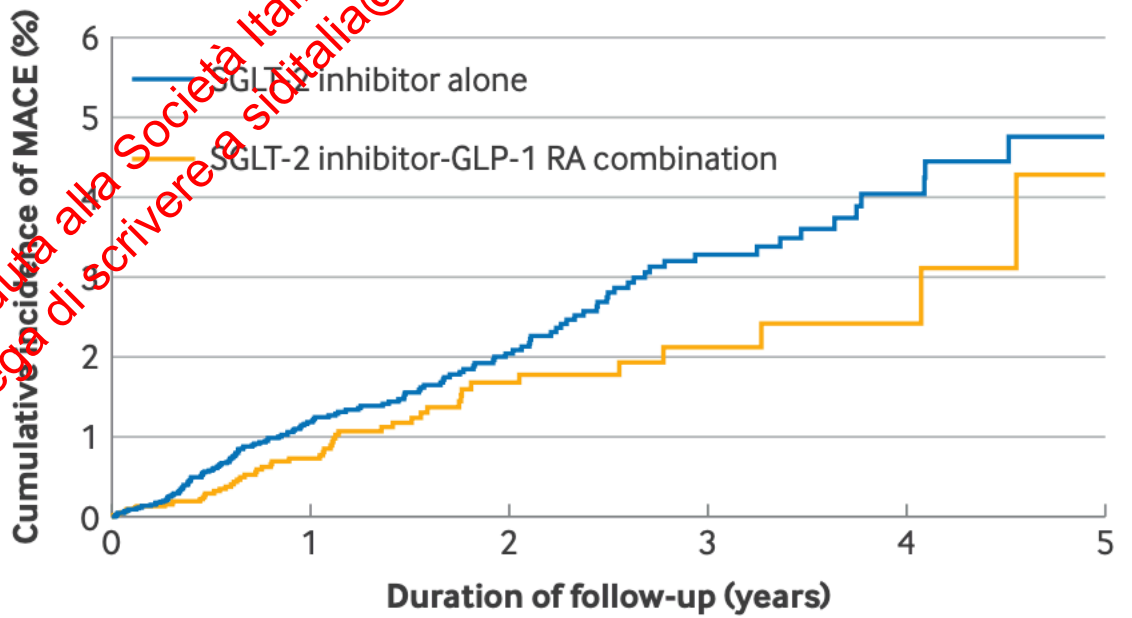
Mantsiou C et al., Diabetes Obes Metab 2020

SGLT2i+GLP-1Ra is superior for MACE



No at risk

GLP-1 RA alone	6696	3798	1996	1072	532	242
GLP-1 RA-SGLT-2 inhibitor combination	6696	1986	1000	599	259	114



No at risk

SGLT-2 inhibitor alone	8942	4732	2347	1146	514	176
SGLT-2 inhibitor-GLP-1 RA combination	8942	2556	1035	428	157	48

Simms-Williams N et al., BMJ 2024

Outline

1. Introduction
2. SGLT2i
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4. Combination therapy
5. Conclusions

Conclusions

- Diabetes is a risk factor for CVD events and death
- SGLT2i/GLP-1Ra combination therapy is the new must To reduces cardiovascular events, improves glycemic control and contributes to weight loss in patients with DM
- New combination therapies open new opportunities for effective therapy

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FONDAZIONE ROMEO ED ENRICA INVERNIZZI

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