SID
Società Italiana di Diabetologia
fondata nel 1964

ROMA | 21 MAGGIO 2019

TEAM DIABETE
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Terapia con analoghi del GLP-1:

e protezione cardiovascolare

disclosure

Il dr. Andrea Giaccari dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Amgen
- Astra Zeneca
- Boehringer Ingelheim
- Eli-Lilly
- MSD
- Sanofi

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.).

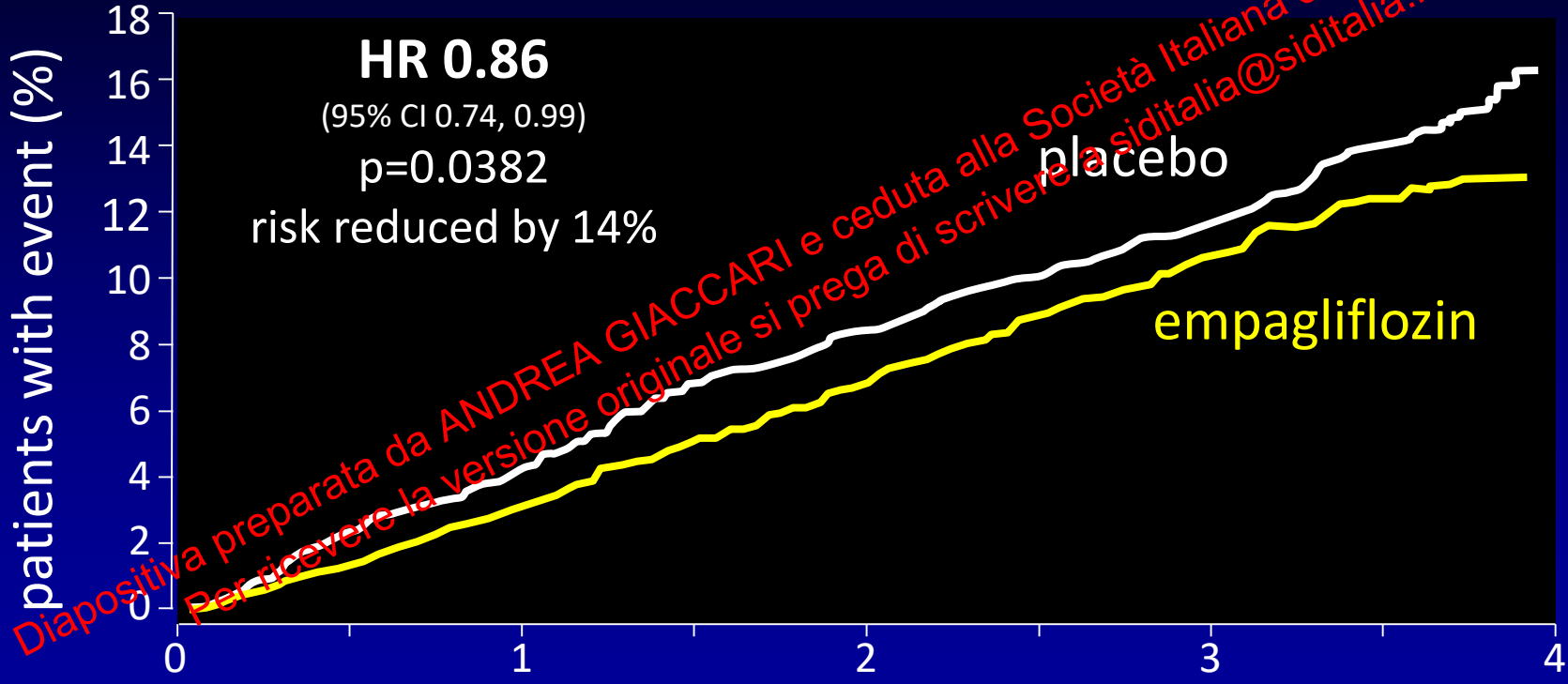
2013 ADA/EASD position statement: Focus on HbA_{1c} status with no drug class preference

[a]Consider initial therapy at this stage when HbA_{1c} is ≥9% (≥75 mmol/mol); [b]Consider initial therapy at this stage when blood glucose is ≥300–350 mg/dL (≥16.7–19.4 mmol/L) and/or HbA_{1c} ≥10–12% (≥86–108 mmol/mol), especially if patient is symptomatic or if catabolic features (weightloss, ketosis) are present, in which case basal insulin + mealtime insulin is the preferred initial regimen; [c]Usually a basal insulin (e.g. neutral protamine Hagedorn, glargine, detemir, degludec); ADA, American Diabetes Association; DPP-4i, dipeptidyl peptidase-4 inhibitor; EASD, European Association for the Study of Diabetes; fx, fracture; GLP-1 RA, glucagon-like peptide-1 receptor agonist; GI, gastrointestinal; GU, genitourinary; HbA_{1c}, glycated hemoglobin; HF, heart failure; SGLT2i, sodium–glucose co-transporter 2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione

Inzucchi SE, et al. *Diabetes Care* 2015;38:140–149

EMPAREG: MACE (primary outcome)

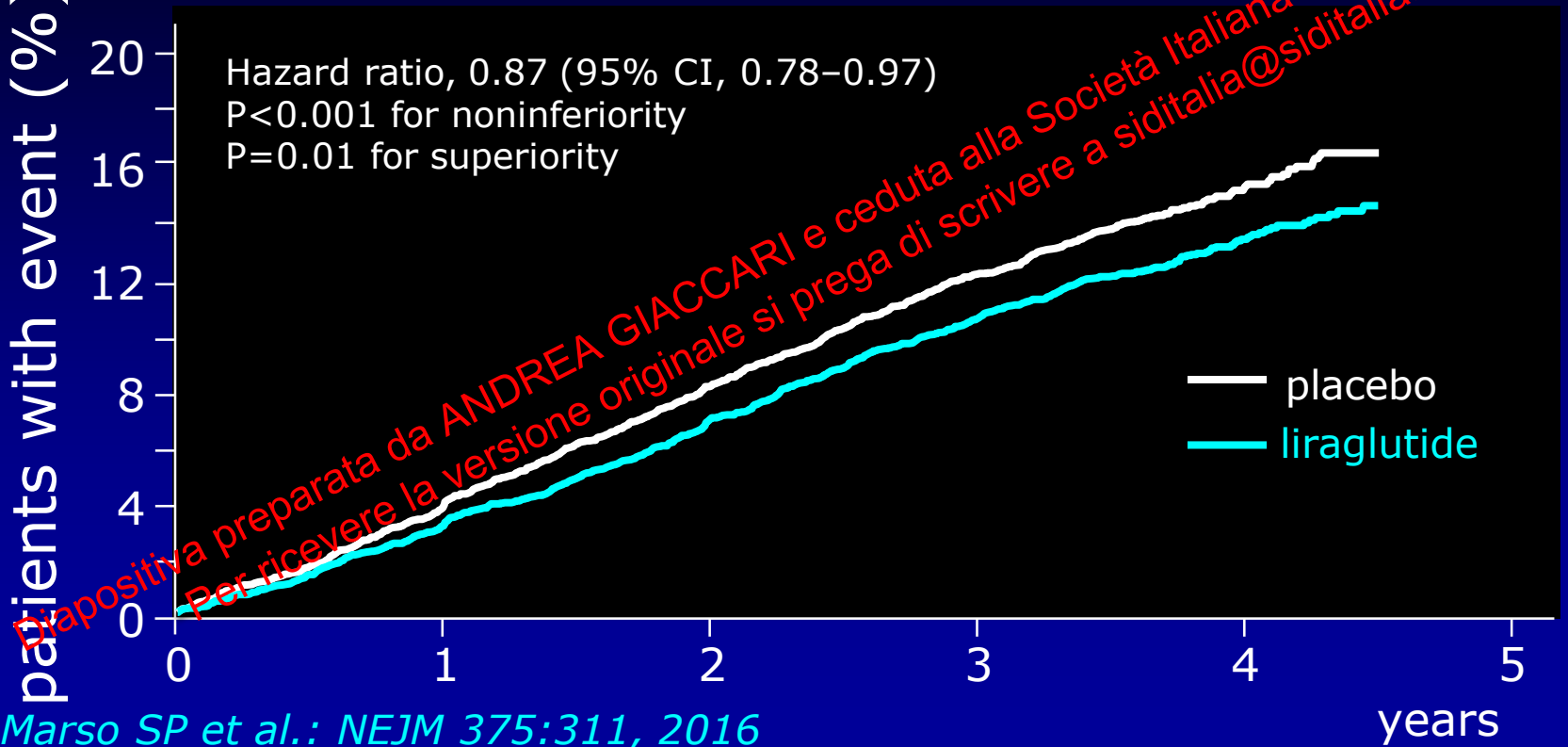
CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke



Zinman B et al.: NEJM 373:2117, 2015

LEADER: MACE (primary outcome)

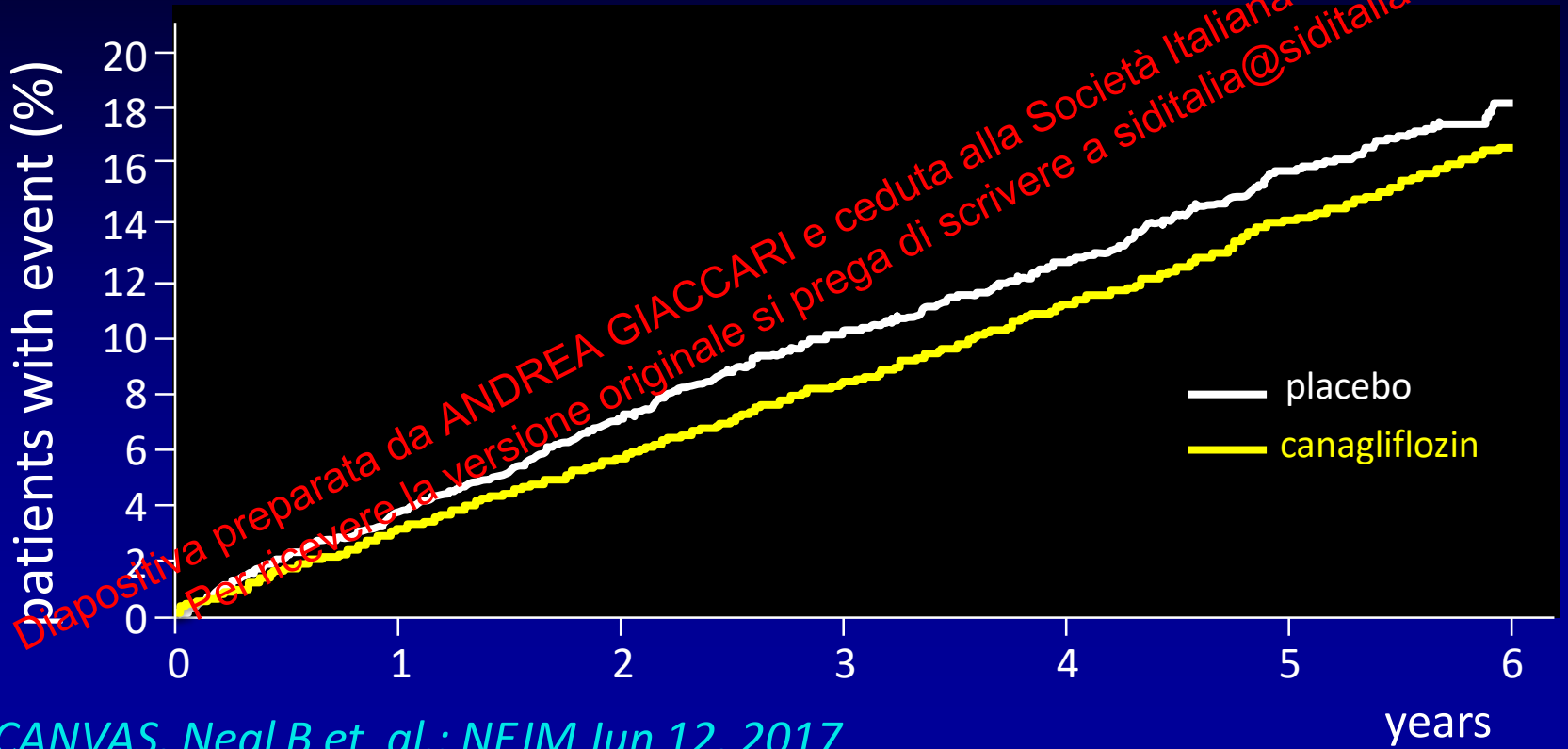
CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke



Marso SP et al.: NEJM 375:311, 2016

CANVAS: MACE (primary outcome)

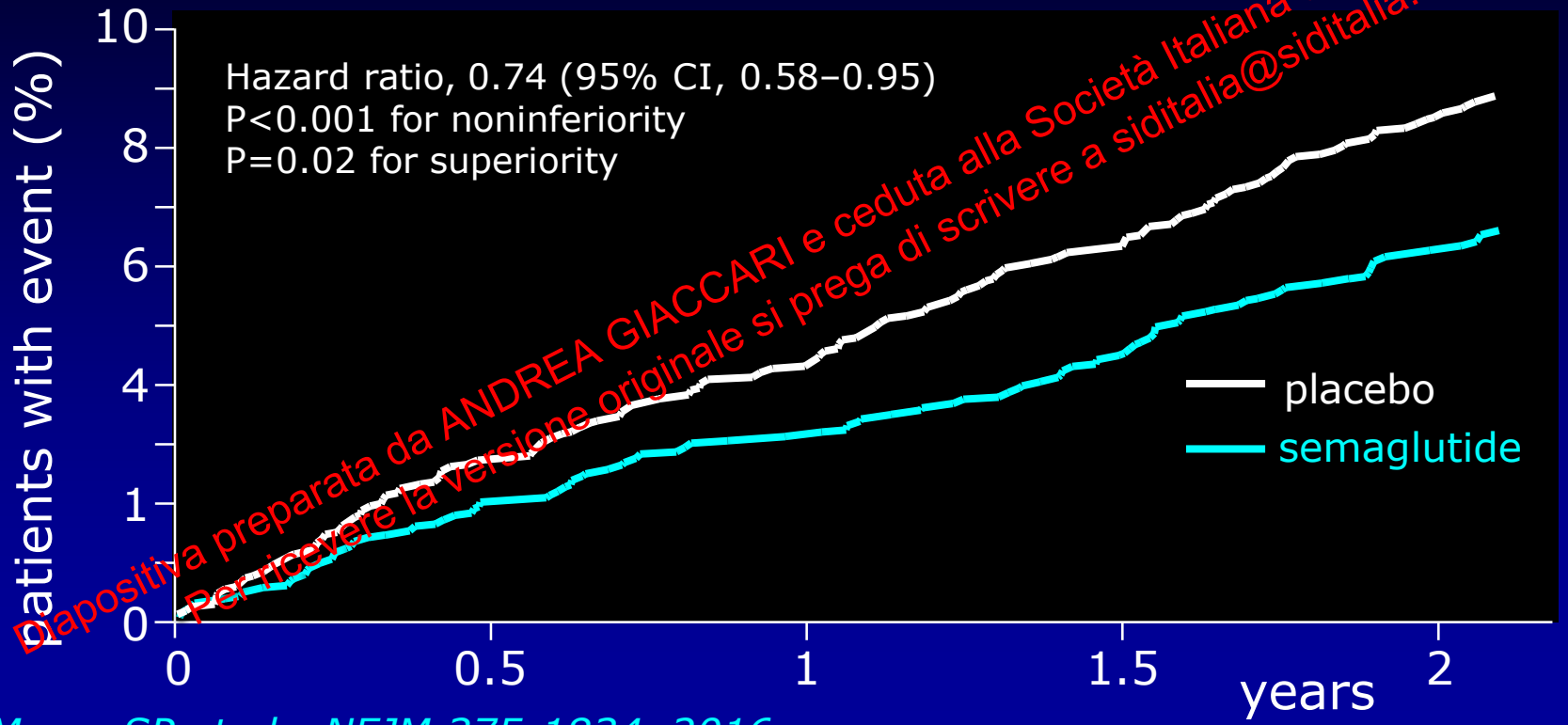
CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke



CANVAS, Neal B et al.: NEJM Jun 12, 2017

SUSTAIN6: MACE (primary outcome)

CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke



Marso SP et al.: NEJM 375:1834, 2016

Step 1: assess cardiovascular disease

Presence of cardiovascular disease is compelling indication

ASCVD PREDOMINATES

GLP-1 RA with proven CVD benefit[1]

either or

SGLT2-i with proven CVD benefit[1-2] if eGFR adequate

if HbA1c above target

if further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2-i, choose agents demonstrating CV safety:

- consider adding the other class with proven CVD benefit
- DPP4i if not on GLP-1 RA
- basal insulin[4]
- TZD[5]
- SU[6]

HEART FAILURE OR CKD PREDOMINATES

SGLT2-i with proven HF and/or CKD and CVD benefit[2-3] if eGFR adequate

or

GLP-1 RA with proven CVD benefit1 if SGLT-2i not tolerated or eGFR less than adequate

if HbA1c above target

- Avoid TZD

Choose agents demonstrating CV safety:

- consider adding the other class with proven CVD benefit[1]
- DPP4i (not saxagliptin) if not on GLP-1 RA
- basal insulin[4]
- SU[6]

1. SGLT2-i = empagliflozin preferred, GLP-1 RA = liraglutide preferred. Proven CVD benefit means it has label indication of reducing CVD events. 2. Be aware that SGLT2-i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use. 3. Both empagliflozin and canagliflozin have shown reduction in HF in CVOT trial. 4. Degludec or U100 glargine have demonstrated CVD safety. 5. Low dose may be better though less well studied for CVD effect. 6. Choose later generation SU with lower risk of hypoglycaemia.

ADA/EASD

FIRST-LINE THERAPY IS METFORMIN AND COMPREHENSIVE LIFESTYLE (INCLUDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY)
IF HbA_{1c} ABOVE TARGET PROCEED AS BELOW

TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

ESTABLISHED ASCVD OR CKD

ASCVD PREDOMINATES

EITHER/OR

- GLP-1 RA with proven CVD benefit[1]
- SGLT2i with proven CVD benefit[1], if eGFR adequate[2]

If HbA_{1c} above target

If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:

- Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
- DPP-4i if not on GLP-1 RA
- Basal insulin[4]
- TZD[5]
- SU[6]

HF OR CKD PREDOMINATES

PREFERABLY
SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[3]

OR

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1 RA with proven CVD benefit[1]

If HbA_{1c} above target

- Avoid TZD in the setting of HF

Choose agents demonstrating CV safety:

- Consider adding the other class with proven CVD benefit[1]
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
- Basal insulin[4]
- SU[6]

NO

WITHOUT ESTABLISHED ASCVD OR CKD

COMPELLING NEED TO MINIMISE HYPOGLYCAEMIA

DPP-4i	GLP-1 RA	SGLT2i[2]	TZD
If HbA_{1c} above target			
SGLT2i[2] **OR** TZD	SGLT2i[2] **OR** TZD	GLP-1 RA **OR** DPP-4i **OR** TZD	SGLT2i[2] **OR** DPP-4i **OR** GLP-1 RA

If HbA_{1c} above target

Continue with addition of other agents as outlined above

If HbA_{1c} above target

Consider the addition of SU[6] **OR** basal insulin:

- Choose later generation SU with lower risk of hypoglycaemia
- Consider basal insulin with lower risk of hypoglycaemia[7]

GAIN OR PROMOTE WEIGHT LOSS

EITHER/OR

- GLP-1 RA with good efficacy for weight loss[8]
- SGLT2i[2]

If HbA_{1c} above target

- SGLT2i[2]
- GLP-1 RA with good efficacy for weight loss[8]

If HbA_{1c} above target

If triple therapy required or SGLT2i and/or GLP-1 RA not tolerated or contraindicated use regimen with lowest risk of weight gain

PREFERABLY

DPP-4i (if not on GLP-1 RA) based on weight neutrality

If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:

- SU[6]
- TZD[5]
- Basal insulin

COST IS A MAJOR ISSUE[9-10]

- SU[6]
- TZD[10]

If HbA_{1c} above target

- TZD[10]
- SU[6]

If HbA_{1c} above target

- **Insulin therapy** basal insulin with lowest acquisition cost

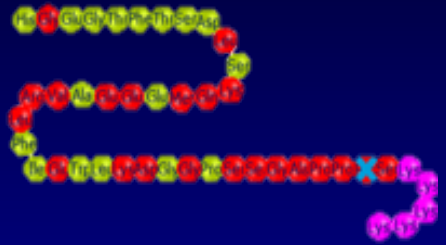
OR

- Consider DPP-4i **OR** SGLT2i with lowest acquisition cost[10]

differences among GLP-1 RAs

exendin based

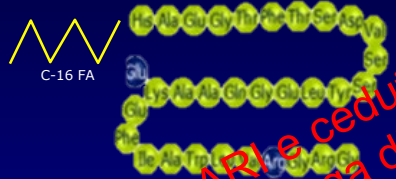
lixisenatide



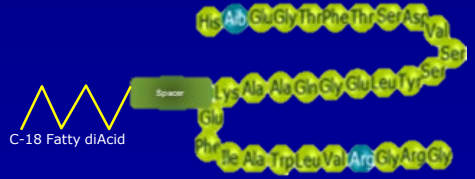
exenatide

acylated GLP-1

liraglutide

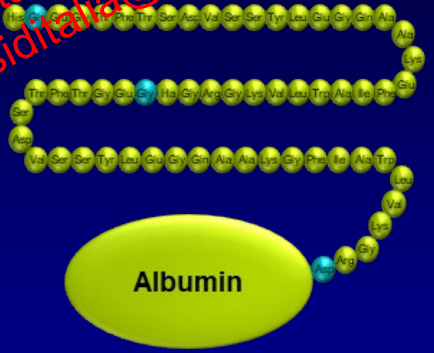


semaglutide

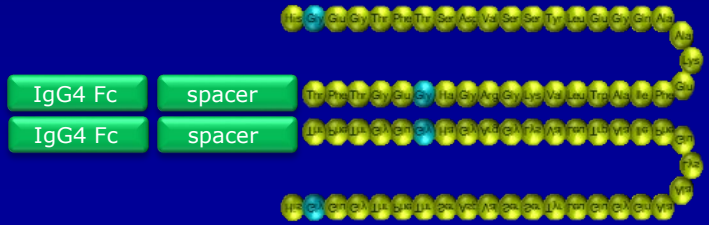


dual GLP-1

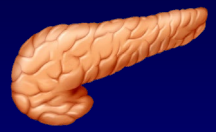
albiglutide

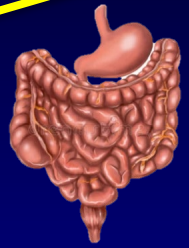


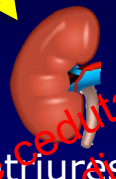
dulaglutide

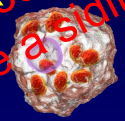


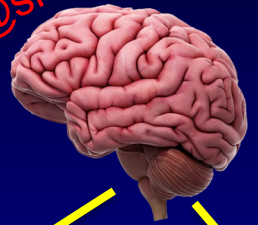
potential cardiovascular effects of GLP-1 RAs











⬆ insulin
⬇ glucagon

⬇ circulating TAGs

⬆ natriuresis
⬇ blood volume

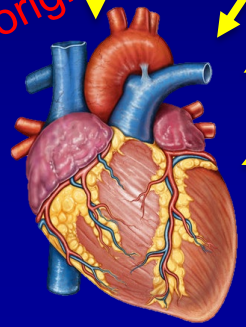
⬇ inflammation

⬇ appetite

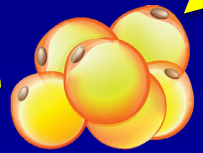
⬇ SNS activity

⬇ body weight

improved heart metabolism



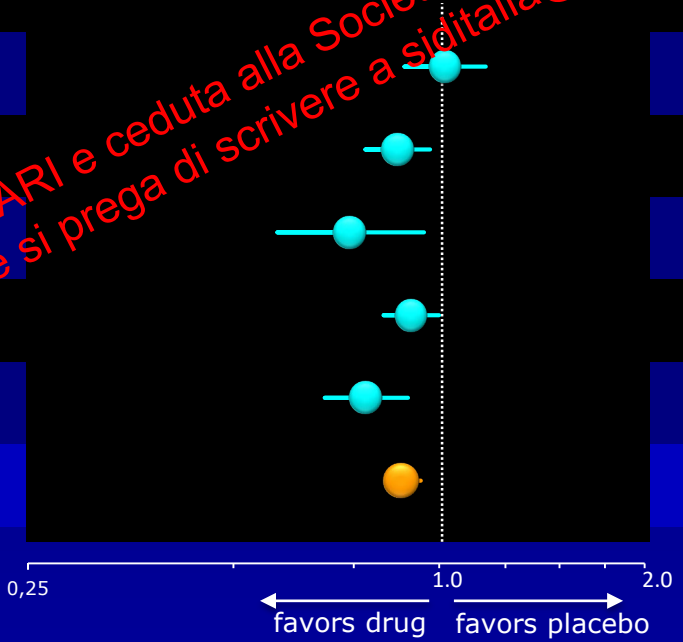
adipokines



modified from Ussher JR and Drucker DJ. Circulation Research 114:1803, 2014

Meta-analysis of GLP1-RAs and SGLT-2is trials on MACE
(non fatal MI, stroke, and CV death)

	Patients	Events	Treatment n/N	Placebo n/N	Weight	HR (95% CI)
ELIXA	6068	805	406/3034	399/3034	16.7	1.02 (0.89 - 1.17)
LEADER	9340	1302	608/4668	694/4672	26.3	0.87 (0.78 - 0.97)
SUSTAIN-6	3297	254	108/1648	146/1649	5.1	0.74 (0.58 - 0.95)
EXSCEL	14752	1744	839/7356	905/7396	36.0	0.91 (0.83 – 1.00)
HARMONY	9463	766	338/4731	428/4732	15.9	0.78 (0.68 - 0.90)
all GLP-1 RA						0.88 (0.84 - 0.94)



Zelniker TA et al.: Circulation 139:2022, 2019 doi: 10.1161/CIRCULATIONAHA.118.038868

Pooled GLP1-RA trials for the composite of myocardial infarction, stroke, and cardiovascular death (MACE)

Trial pra… aziende… molti S… | farmaco tolto dal commercio; 100% eCVD (molto breve) | Trial disegnato nella sola sicurezza (… superiorità presente ma non attesa)

Drug						…ARE	…iflozin	
Median follow-up time, y	2.1	3.8	2.1	3.2	1.6	3.1	2.4	4.2
Trial participants, n	6068	9340	3297	14.752	9463	7020	10142	17.160
Age, y, mean	60.3	64.3	64.6	62	64.1	63.1	63.3	63.9
Female sex, n (%)	2894 (30.7)	3337 (35.7)	1295 (39.3)	5603 (38.0)	2894 (30.6)	2004 (28.5)	3633 (35.8)	6422 (37.4)
Patients with established atherosclerotic CVD, n (%)	6068 (100)	6775 (72.5)	2735 (83.0)	10.782 (73.1)	9463 (100)	7020 (100)	6656 (66)	6974 (41)
History of heart failure, n (%)	1922 (20.3)	1667 (17.8)	777 (23.6)	2389 (16.2)	1922 (20.3)	706 (10.1)	1461 (14.4)	1724 (10.0)
eGFR <60 ml/min/1.73 m2, n (%)	1407 (23.2)	2158 (23.1)	939 (28.5)	3191 (21.6)	NA	1819 (25.9)	2039 (20.1)	1265 (7.4)

The CANVAS Program consisted of 2 trials, the CANVAS and CANVAS-R trials, but they are presented combined. CANVAS Program indicates Canagliflozin Cardiovascular Assessment Study Program; DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58; eGFR, estimated glomerular filtration rate; ELIXA, Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 (Lixisenatide); EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; GLP1-RA, glucagon-like peptide 1 receptor agonist; HARMONY, Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; NA, not applicable; SGLT2i, sodium-glucose contransporter-2 inhibitor; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes.

Zelniker TA et al.: Circulation 139:2022, 2019 doi: 10.1161/CIRCULATIONAHA.118.038868

domanda 1:

Alcuni GLP-1 RAs hanno dimostrato riduzione dei MACE.

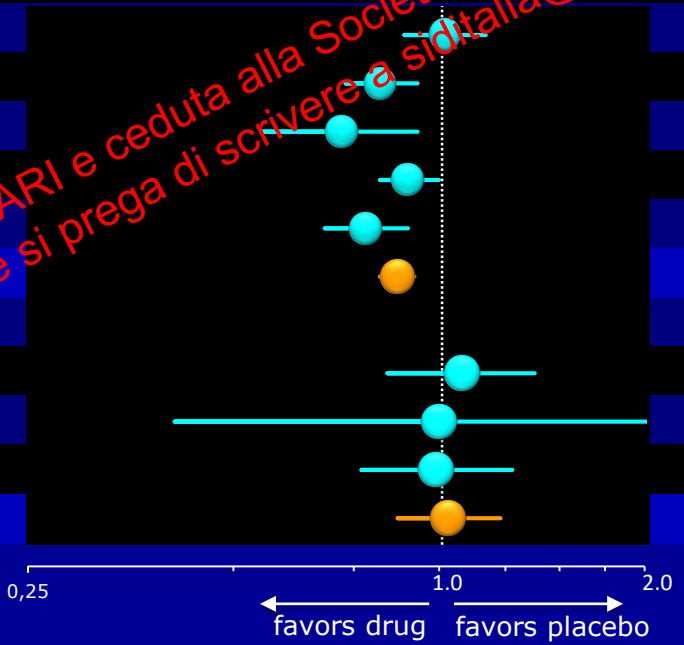
Tale riduzione è presente:

a. solo in pazienti con malattia CV
b. anche in pazienti senza malattia CV
c. è indifferente (in tutti i pazienti)
d. dipende dal farmaco

Meta-analysis of GLP1-RAs and SGLT-2is trials on MACE

stratified by presence of established CVD

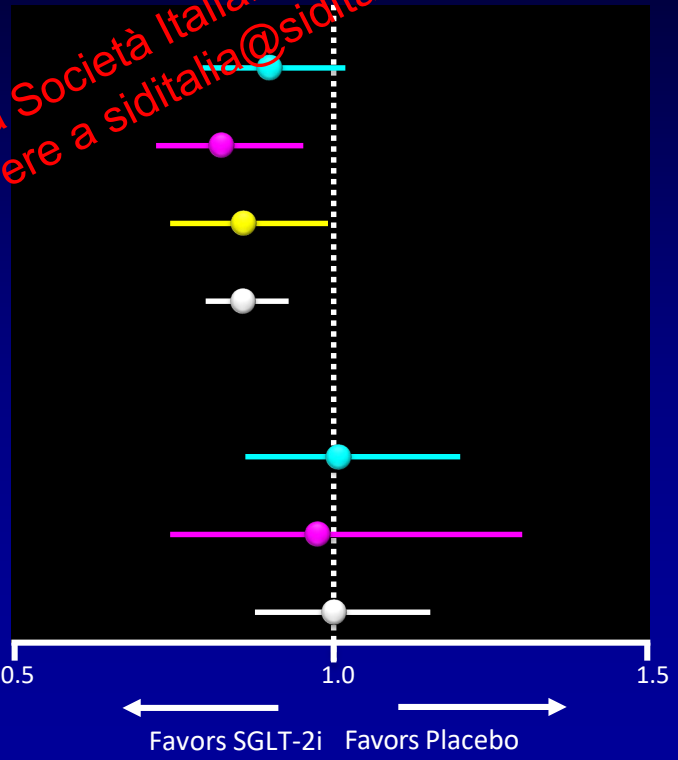
	Patients	Events	Treatment n/N	Placebo n/N	Weight	HR (95% CI)
ELIXA	6068	805	406/3034	399/3034	18.5	1.02 (0.89 - 1.17)
LEADER	6775	1051	480/3403	571/3372	23.6	0.82 (0.73 - 0.93)
SUSTAIN-6	2735	235	98/1353	137/1382	5.0	0.72 (0.55 - 0.93)
EXSCEL	10782	1508	722/5394	786/5388	35.2	0.90 (0.82 – 1.00)
HARMONY	9463	766	338/4731	428/4732	17.6	0.78 (0.68 - 0.90)
eCVD						0.87 (0.82 - 0.92)
LEADER	2565	251	128/1265	123/1300	49.2	1.08 (0.84 - 1.38)
SUSTAIN-6	562	19	10/295	9/267	3.8	1.00 (0.41 - 2.46)
EXSCEL	3970	236	117/1962	119/2008	47.0	0.99 (0.77 - 1.28)
MRF						1.03 (0.87 - 1.23)



Zelniker TA et al.: Circulation 139:2022, 2019 doi: 10.1161/CIRCULATIONAHA.118.038868

SGLT-2 inhibitors reduce MACE in T2D patients with established CV but not in patients with Multiple Risk Factors

	events	Treatment events per 1000 P-Y	Placebo events per 1000 P-Y	HR (95% CI)
eCVD				
DECLARE	1020	36.8	41.0	0.90 (0.79 - 1.02)
CANVAS	796	34.1	41.3	0.86 (0.74 - 0.99)
EMPA-REG	772	37.4	43.9	0.82 (0.72 - 0.95)
all eCVD				0.86 (0.80 - 0.93)
MRF				
DECLARE	539	13.4	13.3	1.01 (0.86 - 1.20)
CANVAS	215	15.8	15.5	0.98 (0.74 – 1.30)
all MRF				1.00 (0.87 - 1.16)



Zelniker TA, et al. Lancet 393:31, 2019

REWIND press release

[redacted] (dulaglutide) demonstrates superiority in reduction of cardiovascular events for broad range of people with type 2 diabetes

November 5, 2018

Only 31 percent of REWIND trial participants had established CV disease

INDIANAPOLIS, Nov. 5, 2018 /PRNewswire/ - [redacted]® (dulaglutide) significantly reduced major adverse cardiovascular events (MACE), a composite endpoint of cardiovascular (CV) death, non-fatal myocardial infarction (heart attack) or non-fatal stroke, meeting the primary efficacy objective in the precede[redacted] type 2 diabetes medicine to demonstrate superiority [redacted]id not have established CV disease.

The study included a ma[redacted]onist class. REWIND assessed the risk of MACE in adu[redacted]eekly Trulicity 1.5 mg to placebo when added to standard[redacted]

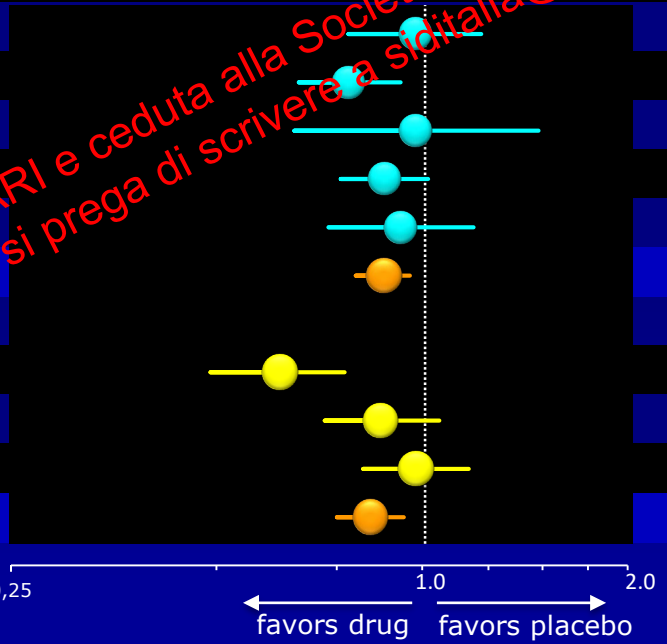
"The REWIND study wa[redacted]encing an initial cardiovascular event, and prevent futur[redacted]MSc, FRCPC, professor of medicine and deputy director of the Population Health Institute at McMaster University and Hamilton Health Sciences, and REWIND study chair. "The MACE reduction demonstrated by [redacted], across a broad range of people with type 2 diabetes, is compelling and we look forward to analyzing and reporting all of the data[redacted]

REWIND is distinct compared to other CV outcome trials due to the limited number of people with established CV disease who participated in the trial, allowing [redacted]'s CV effect to be measured in a broad population of people with type 2 diabetes. Importantly, REWIND had a median follow-up period of more than 5 years, the longest for a CV outcome trial in the GLP-1 receptor agonist class. In comparison, other CV outcome trials had more people with a higher baseline A1C and a greater percentage of patients who had established CV disease. Of the 9,901 REWIND participants, the mean baseline A1C was relatively lower at 7.3 percent, and only 31 percent had established CV disease.

~70% dei pazienti in prevenzione primaria
riduzione significativa MACE
9901 soggetti per 5 anni
HbA1c basale 7.3
ADA 2019

Meta-analysis of GLP1-RAs and SGLT-2is trials on **CV death** stratified by drug class

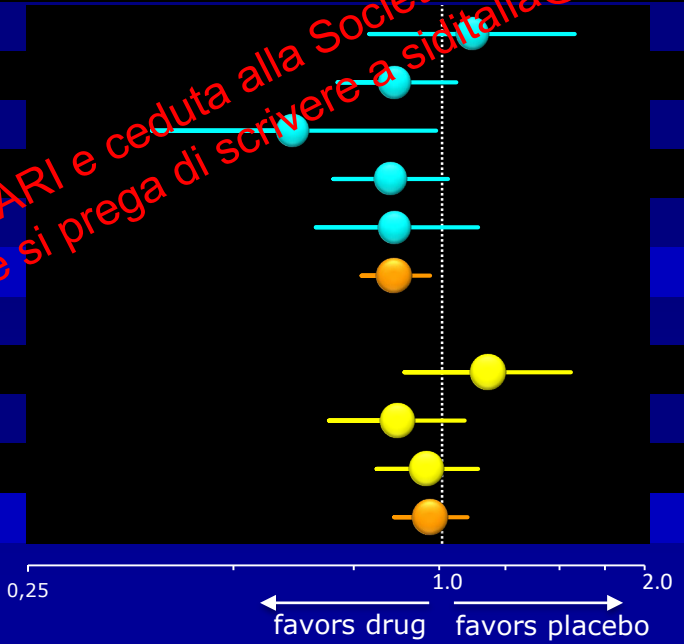
	Patients	Events	Treatment events per 100 ptyrs	Placebo events per 100 ptyrs	Weight	HR (95% CI)
ELIXA	6068	314	2.3	2.4	16.3	0.98 (0.78 - 1.22)
LEADER	9340	497	1.2	1.6	27.7	0.78 (0.66 - 0.93)
SUSTAIN-6	3297	90	1.4	1.3	4.8	0.98 (0.65 - 1.48)
EXSCEL	14752	723	1.4	1.5	37.6	0.88 (0.76 - 1.02)
HARMONY	9463	252	1.6	1.7	13.6	0.93 (0.73 - 1.19)
GLP-1 RA						0.88 (0.80 - 0.96)
EMPAREG	7020	309	1.2	2.0	25.1	0.62 (0.49 - 0.77)
CANVAS	10142	453	1.2	1.3	34.3	0.87 (0.72 - 1.06)
DECLARE	17160	494	0.7	0.7	40.6	0.98 (0.82 - 1.17)
SGLT-2 i						0.84 (0.75 - 0.94)



Zelniker TA et al.: Circulation 139:2022, 2019 doi: 10.1161/CIRCULATIONAHA.118.038868

Meta-analysis of GLP1-RAs and SGLT-2is trials on **stroke** stratified by drug class

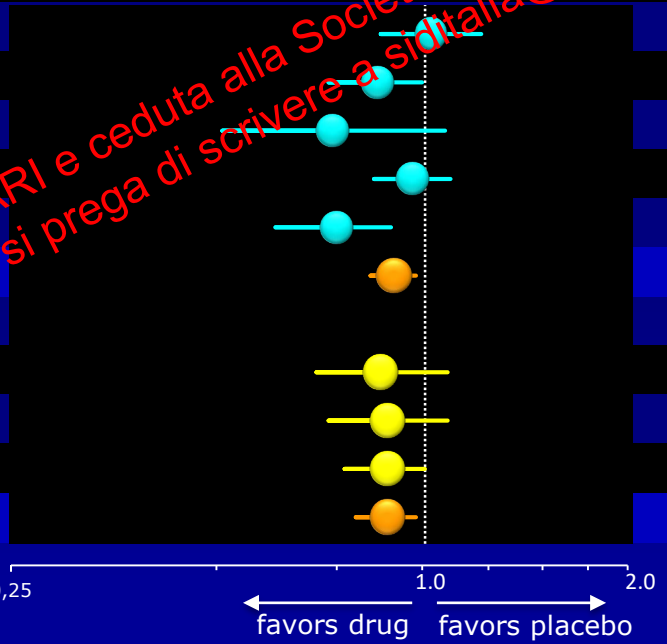
	Patients	Events	Treatment events per 100 ptyrs	Placebo events per 100 ptyrs	Weight	HR (95% CI)
ELIXA	6068	127	1.0	0.9	10.7	1.12 (0.79 - 1.58)
LEADER	9340	372	1.0	1.1	32.0	0.86 (0.71 - 1.06)
SUSTAIN-6	3297	71	0.8	1.3	5.6	0.61 (0.38 - 0.99)
EXSCEL	14752	405	0.8	0.9	34.5	0.85 (0.70 - 1.03)
HARMONY	9463	202	1.2	1.4	17.2	0.86 (0.66 - 1.14)
GLP-1 RA						0.86 (0.77 - 0.97)
EMPAREG	7020	233	1.2	1.0	19.2	1.18 (0.89 - 1.56)
CANVAS	10142	389	0.8	1.0	29.0	0.87 (0.69 - 1.09)
DECLARE	17160	518	0.8	0.8	51.8	0.96 (0.81 - 1.14)
SGLT-2 i						0.97 (0.86 - 1.10)



Zelniker TA et al.: Circulation 139:2022, 2019 doi: 10.1161/CIRCULATIONAHA.118.038868

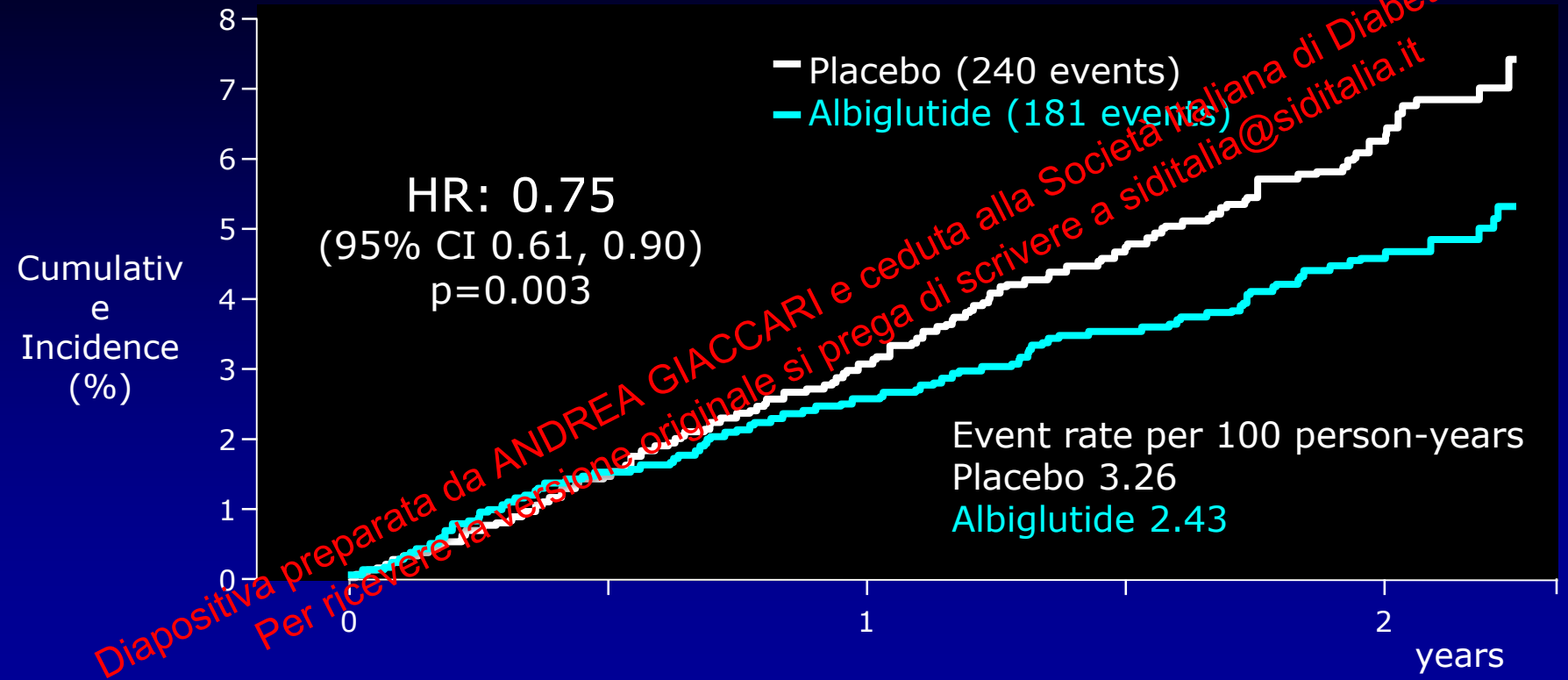
Meta-analysis of GLP1-RAs and SGLT-2is trials on **MI** stratified by drug class

	Patients	Events	Treatment events per 100 ptyrs	Placebo events per 100 ptyrs	Weight	HR (95% CI)
ELIXA	6068	531	4.2	4.1	20.7	1.03 (0.87 - 1.22)
LEADER	9340	631	1.6	1.9	23.9	0.86 (0.73 – 1.00)
SUSTAIN-6	3297	111	1.4	1.9	4.2	0.74 (0.51 - 1.08)
EXSCEL	14752	976	2.1	2.1	35.6	0.97 (0.85 - 1.10)
HARMONY	9463	421	2.4	3.3	15.6	0.75 (0.61 – 0.90)
GLP-1 RA						0.91 (0.84 – 0.98)
EMPAREG	7020	221	0.9	1.4	24.0	0.87 (0.70 - 1.09)
CANVAS	10142	243	0.6	0.9	25.6	0.89 (0.73 - 1.09)
DECLARE	17160	498	0.6	0.8	50.4	0.89 (0.77 - 1.01)
SGLT-2 i						0.89 (0.80 - 0.98)



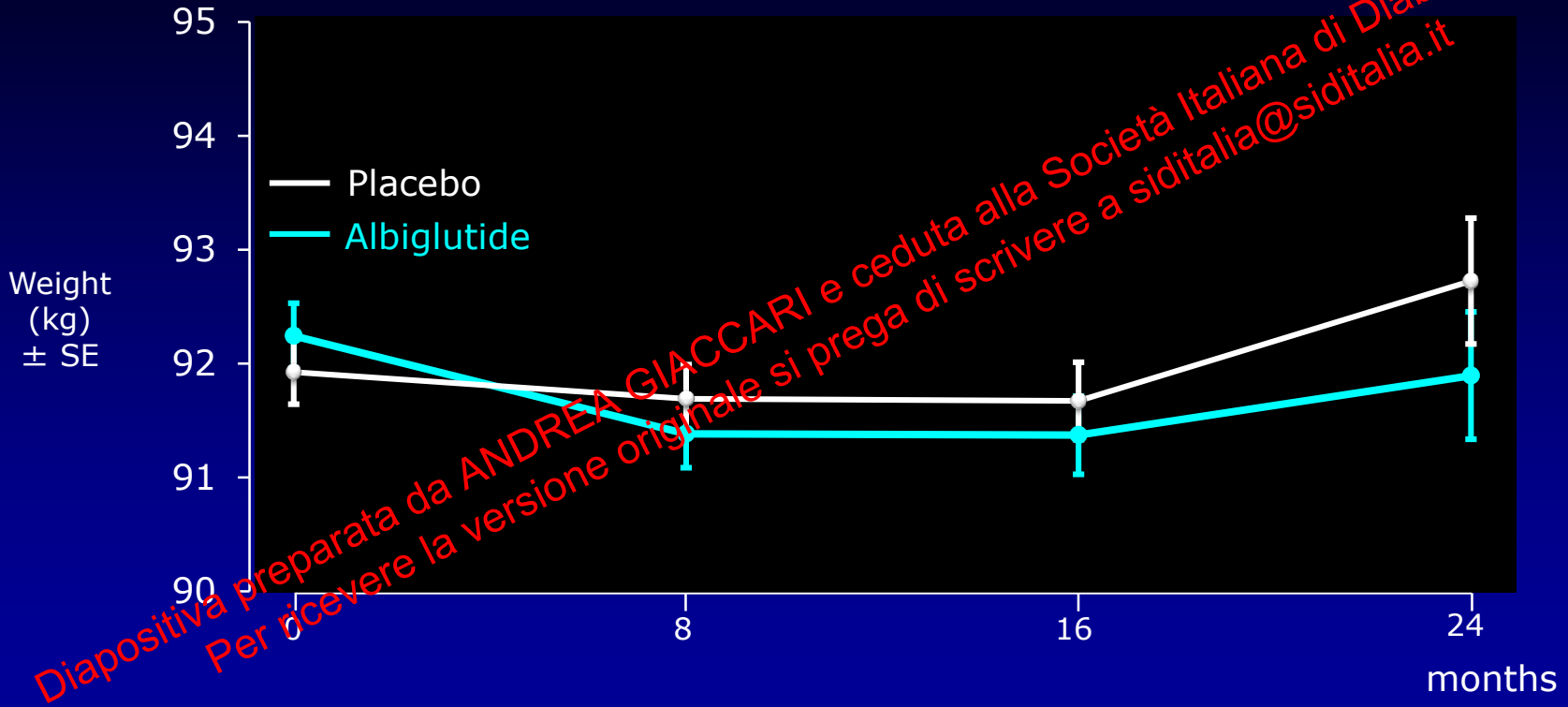
Zelniker TA et al.: Circulation 139:2022, 2019 doi: 10.1161/CIRCULATIONAHA.118.038868

HARMONY: myocardial infarction, fatal + non-fatal



Hernandez AF et al.: Lancet 392:1519, 2018 doi: 10.1016/S0140-6736(18)32261-X

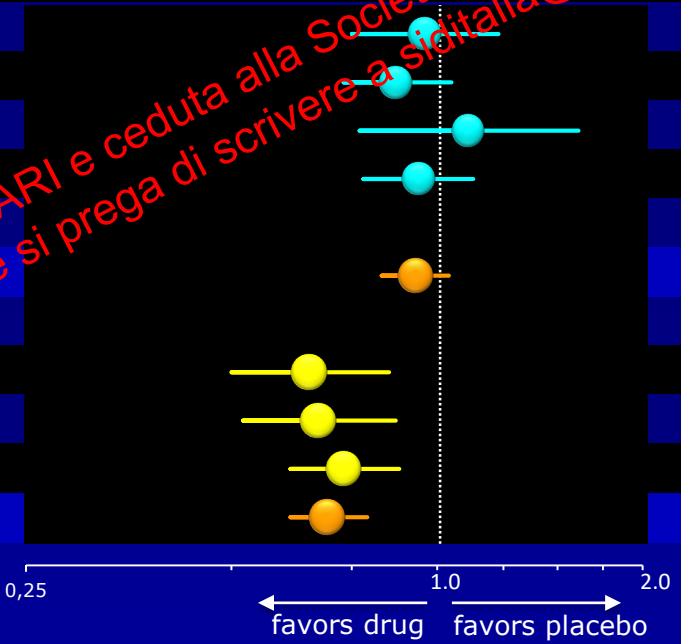
HARMONY: mean body weight over time



Hernandez AF et al.: Lancet 392:1519, 2018 doi: 10.1016/S0140-6736(18)32261-X

Meta-analysis of GLP1-RAs and SGLT-2is trials on **hHF** stratified by drug class

	Patients	Events	Treatment events per 100 ptyrs	Placebo events per 100 ptyrs	Weight	HR (95% CI)
ELIXA	6068	249	1.8	1.9	19.7	0.96 (0.75 - 1.23)
LEADER	9340	466	1.2	1.4	36.4	0.87 (0.73 - 1.05)
SUSTAIN-6	3297	113	1.8	1.6	8.8	1.11 (0.77 - 1.61)
EXSCEL	14752	450	0.9	1	35.0	0.94 (0.78 - 1.13)
HARMONY						
GLP-1 RA						0.93 (0.83 - 1.04)
EMPAREG	7020	221	0.9	1.4	24.0	0.65 (0.50 - 0.85)
CANVAS	10142	243	0.6	0.9	25.6	0.67 (0.52 - 0.87)
DECLARE	17160	498	0.6	0.8	50.4	0.73 (0.61 - 0.88)
SGLT-2 i						0.69 (0.61 - 0.79)



Zelniker TA et al.: Circulation 139:2022, 2019 doi: 10.1161/CIRCULATIONAHA.118.038868

domanda 2:

Alcuni GLP-1 RAs hanno dimostrato riduzione di endpoint compositi renali.

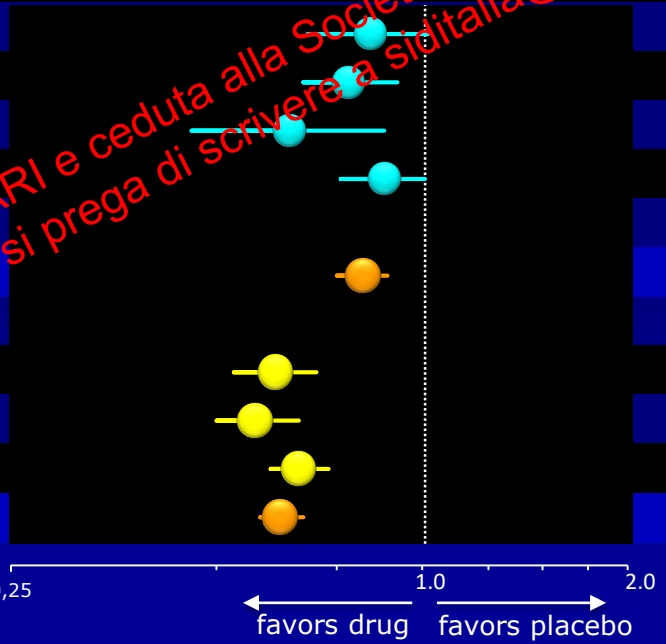
Tale riduzione è soprattutto dovuta a:

a. riduzione progressione albuminuria
b. riduzione aumento creatinina (ridotto eGFR)
c. a + b
d. non è distinguibile

Meta-analysis of GLP1-RAs and SGLT-2is trials on CKD

composite renal endpoint **with** macroalbuminuria stratified by drug class

	Patients	Events	Treatment n/N	Placebo n/N	Weight	HR (95% CI)
ELIXA	5286	375	203/2639	172/2647	20.0	0.84 (0.68 - 1.02)
LEADER	9340	605	268/4668	337/4672	32.2	0.78 (0.67 - 0.92)
SUSTAIN-6	3297	162	62/1648	100/1649	7.7	0.64 (0.46 - 0.88)
EXSCEL	14752	773	366/6256	407/6222	40.1	0.88 (0.76 - 1.01)
HARMONY						
GLP-1 RA						0.82 (0.75 - 0.89)
EMPAREG	6185	913	525/4124	388/2061	24.9	0.61 (0.53 - 0.70)
CANVAS	10142	844	na	na	25.0	0.57 (0.50 - 0.66)
DECLARE	17160	1675	678/8582	99/8578	50.1	0.66 (0.60 - 0.73)
SGLT-2 i						0.62 (0.58 - 0.67)

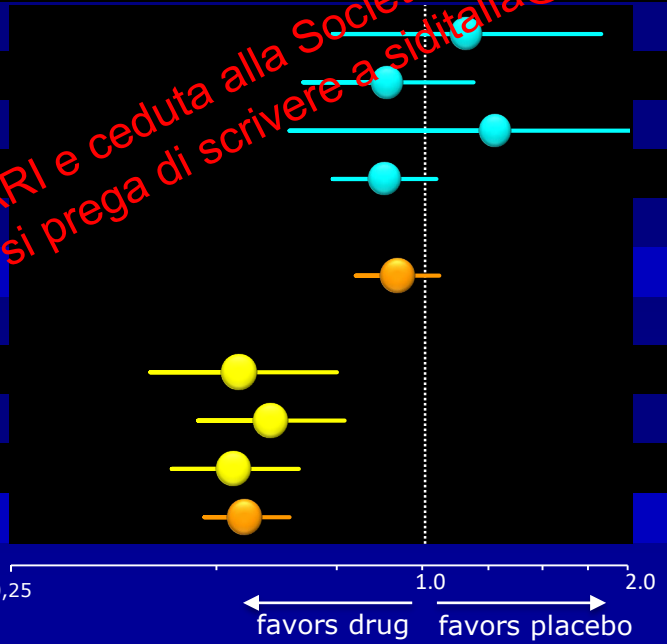


Zelniker TA et al.: Circulation 139:2022, 2019 doi: 10.1161/CIRCULATIONAHA.118.038868

Meta-analysis of GLP1-RAs and SGLT-2is trials on CKD

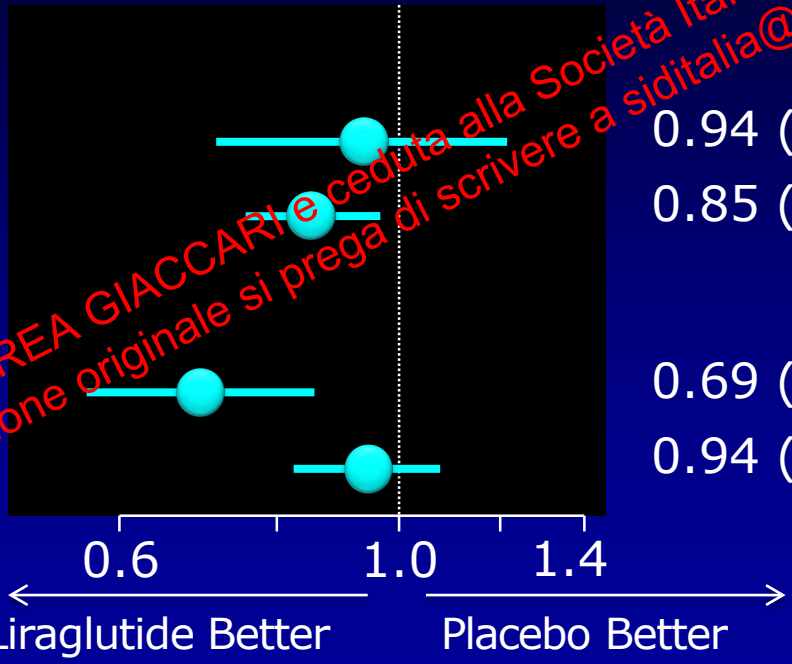
composite renal endpoint **w/o** macroalbuminuria stratified by drug class

	Patients	Events	Treatment n/N	Placebo n/N	Weight	HR (95% CI)
ELIXA	6063	76	35/3032	41/3031	9.5	1.16 (0.74 - 1.83)
LEADER	9340	184	87/4668	97/4672	23.4	0.89 (0.67 - 1.19)
SUSTAIN-6	3297	32	18/1648	14/1649	4.0	1.28 (0.64 - 2.58)
EXSCEL	12914	519	246/6456	273/6458	63.1	0.88 (0.74 - 1.05)
HARMONY						
GLP-1 RA						0.92 (0.80 - 1.06)
EMPAREG	6968	152	61/465	71/2323	20.9	0.54 (0.40 - 0.75)
CANVAS	10142	249	na	na	34.0	0.60 (0.47 - 0.77)
DECLARE	17160	365	127/8582	238/8578	45.1	0.53 (0.43 - 0.66)
SGLT-2 i						0.55 (0.48 - 0.64)



Zelniker TA et al.: Circulation 139:2022, 2019 doi: 10.1161/CIRCULATIONAHA.118.038868

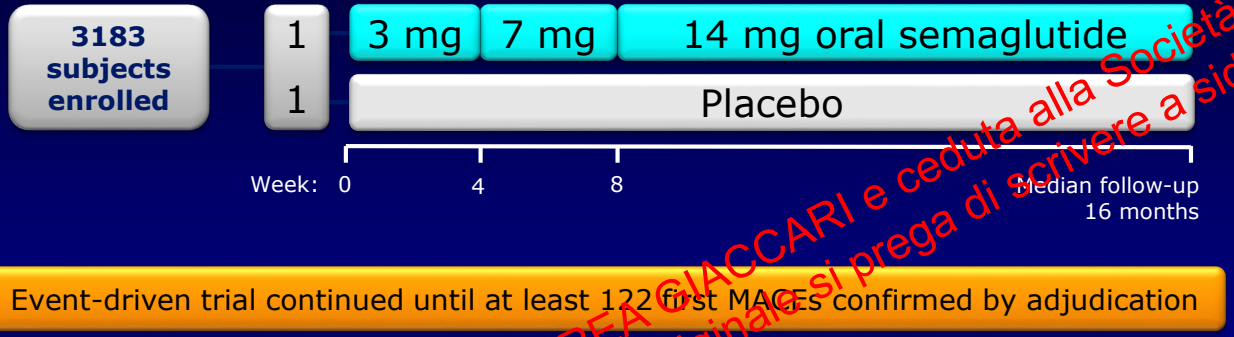
LEADER: group sub-analysis



Marso SP et al.: NEJM 375:311, 2016

PIONEER-6: study design

pre-approval CVOT with oral semaglutide



Primary endpoint

- Time to first MACE (CV death, non-fatal stroke, or non-fatal MI)

Key secondary endpoints

- Time to first occurrence of individual components of MACE
- Time to all-cause mortality
- Time to expanded MACE endpoint

Randomised, double-blind, placebo-controlled trial designed to rule out an excess cardiovascular risk of 80% for oral semaglutide vs. placebo when added to standard of care in subjects with T2D at high risk of CV events

Bain SC et al. DOM 2018; 1-10. doi: 10.1111/dom.13553

PIONEER-6: preliminary outcomes

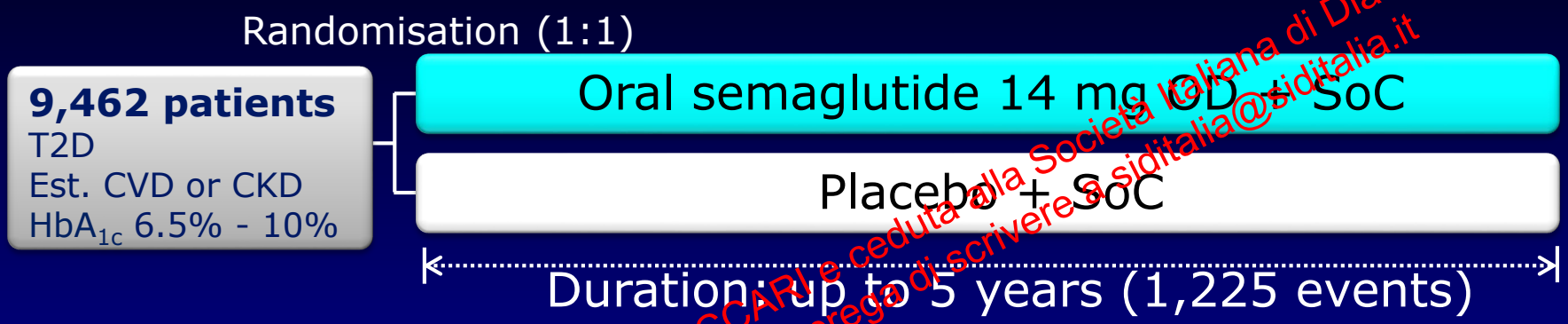
as announced by NN

	Hazard ratio	p value
MACE	0.79	Non-inferiority confirmed; superiority not confirmed
CV death	0.49	p=0.03
Non-fatal MI	1.18	NS
Non-fatal stroke	0.74	NS
All-cause mortality	0.51	p=0.008

CI, confidence interval; CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction; NS, not significant;

Novo Nordisk company announcement: www.novonordisk.com/media

SOUL: study design



Key endpoints

- **Primary:** Cardiovascular death, non-fatal myocardial infarction or non-fatal stroke (MACE)

- **Secondary confirmatory:**
- 5-component composite CKD endpoint consisting of: Cardiovascular death, renal death, onset of macroalbuminuria, 50% reduction in eGFR, onset of eGFR < 15 ml/min/1.73m^2 or initiation of chronic renal replacement therapy
- Cardiovascular Death
- A composite peripheral artery endpoint consisting of: Acute and chronic limb ischemia (MALE)

T2D, type 2 diabetes; CVD, cardiovascular disease; CKD, chronic kidney disease; MACE, major adverse cardiovascular events; SoC, Standard of Care (Will allow all glucose lowering drugs except GLP-1s); MALE, major adverse limb events

Step 1: assess cardiovascular disease

Presence of cardiovascular disease is compelling indication

ASCVD PREDOMINATES

GLP-1 RA with proven CVD benefit[1]

either or

SGLT2-i with proven CVD benefit[1-2] if eGFR adequate

if HbA1c above target

if further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2-i, choose agents demonstrating CV safety:

- consider adding the other class with proven CVD benefit
- DPP4i if not on GLP-1 RA
- basal insulin[4]
- TZD[5]
- SU[6]

HEART FAILURE OR CKD PREDOMINATES

SGLT2-i with proven HF and/or CKD and CVD benefit[2-3] if eGFR adequate

or

GLP-1 RA with proven CVD benefit1 if SGLT-2i not tolerated or eGFR less than adequate

if HbA1c above target

- Avoid TZD

Choose agents demonstrating CV safety:

- consider adding the other class with proven CVD benefit[1]
- DPP4i (not saxagliptin) if not on GLP-1 RA
- basal insulin[4]
- SU[6]

1. SGLT2-i = empagliflozin preferred, GLP-1 RA = liraglutide preferred. Proven CVD benefit means it has label indication of reducing CVD events. 2. Be aware that SGLT2-i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use. 3. Both empagliflozin and canagliflozin have shown reduction in HF in CVOT trial. 4. Degludec or U100 glargine have demonstrated CVD safety. 5. Low dose may be better though less well studied for CVD effect. 6. Choose later generation SU with lower risk of hypoglycaemia.

take home messages

- farmaci diversi, Moa diversi, trial diversi, outcome diversi
- preferibili (ed unici prescrivibili) soprattutto per bassa eGFR
- siamo solo a metà del percorso, ma intanto usiamoli!


Diapositiva preparata da ANDREA GIACCARI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it
navigare necesse